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Effects of the antihistamine pyrrobutamine on soft tissue wound healing

■ *Odus L. Baldridge, Jr., D.D.S., M.S., Detroit*

The effectiveness of antihistamines as an aid to healing oral surgical wounds, originally reported by Silverman[1] in 1952, has been confirmed by Johnson,[2] Maslansky and Maslansky[3] and Buchanan.[4] The conclusions of these investigators were based on clinical observation. It seemed desirable, therefore, to assess the therapeutic merit of these preparations by controlled animal experiments. The present paper reports the results of such experiments together with further clinical observations.

■ *Review of Literature*

The action of histamine in trauma has long been the subject of research. Many symptoms, including shock, can be induced by the injection of histamine. The literature has many references to histamine-like substances which produce a similar reaction.

Kessler and Van Emburgh[5] state that Cannon,[6] in his discussion of the theory of traumatic shock, mentions that the reactions after injury can be regarded as due to a large group of poisonous protein derivatives. These may be products of partial digestion, of bacterial action, or of tissue extraction, and, although proof is still lacking, a substance histamine-like in character may be given off into the blood stream when tissues are severely damaged. The effects of these substances are quite similar to those produced experimentally by histamine. In 1910 Dale[7] pointed out that secondary shock appears to be in the same general category with anaphylactic shock and is probably the

Condensation of a paper prepared in fulfillment of a part of the requirements for a degree of Master of Science in oral surgery, Washington University, St. Louis.

Resident in oral surgery, Henry Ford Hospital.

1. Silverman, R. E. Use of antihistamines in oral surgery. J. Oral Surg. 11:231 July 1953.
2. Johnson, W. B. Antihistamine drugs to inhibit edema following oral surgery. D. Digest 59:314 July 1953.
3. Maslansky, M. M., and Maslansky, L. Injectable antihistamines—an aid in oral surgery. New York D. J. 19:274 June-July 1953.
4. Buchanan, W. T. Antihistamines vs. edema in oral surgery. J. Michigan D. A. 36:41 Feb. 1954.
5. Kessler, M. M., and Van Emburgh, G. H. Use of antihistamines in treatment of surgical and accidental trauma. Indust. Med. 20:567 Dec. 1951.
6. Cannon, W. B. Traumatic shock. In Surgical monographs. New York, Appleton-Century-Crofts, Inc., 1923-1926, p. 152.
7. Dale, H. H. Croonian lectures on some chemical factors in control of the circulation. Lancet 216:1285 June 15, 1929.

consequence of poisoning by protein-cleavage products. Histamine is a protein-cleavage product, a decarboxylation product of the amino acid histidine which is present in all complete protein.[8]

The evidence that traumatic shock is due to liberation of histamine or histamine-like substance is supported by the recent work of Sanders.[9] The original theory advanced by Dale[7] postulated that traumatic shock was the result of a toxemia caused by the liberation of histamine-like substances from the injured region. Sanders, using a new method of quantitative analysis, found a definite rise in blood and saliva histamine on a series of patients immediately after traumatic oral surgical procedures.

Selle[10] has postulated that histamine is bound as a precursor or as an inactive form in most tissue cells of the body. The intracellular reaction between antigen and antibody results in the liberation of histamine or of an H factor. It is also possible that histamine is active in the cells in an easily dissociated form, and that it becomes effective only after damage or irritation of the cell. Kivimäki[11] also states that experiments have proved that histamine creates an expansion of the capillaries, a lowering of blood pressure and damaging of the capillary endothelium. This leads to a flow of plasma into the surrounding tissue, a thickening of blood and an increase of the red blood corpuscles. The expansion of the capillaries and damaging of the endothelium signify an intense disturbance of the circulation.

Feinberg, Malkiel and Feinberg[12] point out that histamines cause capillary dilation followed by localized edema due to the passage of plasma proteins and fluids into the extracellular spaces by virtue of changes in the permeability of the vessel walls.

Salter[8] states that the chief theoretical basis for antihistamine action is the competition of the antihistamines in displacing or replacing histamine in attachment to some cell receptor as yet unknown. Haley and Harris[13] studied the effect of antihistamine drugs on the mammalian capillary bed and concluded that the drugs have a vasoconstrictor action on the precapillary sphincter muscles, whereas histamine has a vasodilator action. They stated further that the vasoconstrictor effect is produced with doses which parallel other animal or human therapeutic doses. They concluded that both histamine and antihistamines act at the same site, that the antihistamine does not decrease the blood level of histamine but simply blocks its action.

Weeks and Gunnar[14] studied the effects of antihistamines on vasodilatation and capillary permeability in chemical and thermal burns in animals. They state that, in their series, vasodilatation was decreased from 25 per cent to 78 per cent. Loew,[15] using the technic of Menkin,[16]

8. Salter, W. T. Textbook of pharmacology. Philadelphia, W. B. Saunders Co., 1952, p. 322.

9. Sanders, S. G. Personal communication.

10. Selle, W. A. Histamine. Texas Rep. Biol. & Med. 4:138, (Summer) 1946.

11. Kivimäki, Juuso. On the influence of antihistamines in operative procedures. Suom. Hammaslääk. Toim. 48:Supp. 1, 13, 1952.

12. Feinberg, S. M.; Malkiel, S. M., and Feinberg, A. R. Antihistamines. Chicago, Year Book Publishers, Inc., 1950, p. 21.

13. Haley, T. J., and Harris, D. H. Effect of topically applied antihistamine drugs on the mammalian capillary bed. J. Pharmacol. & Exper. Therap. 95:293 March 1949.

14. Weeks, R. E., and Gunnar, R. M. Effect of triplelennamine hydrochloride on acute inflammation. Arch. Path. 48:178 Aug. 1949.

15. Loew, E. R. Pharmacology of antihistamine compounds. Physiol. Rev. 27:542 Oct. 1947.

16. Menkin, V. Studies on inflammation. J. Exper. Med. 64:485 Sept. 1936.

showed that at least some of the outstanding antihistamines counteracted the characteristic increase in capillary permeability induced by histamine locally. Halpern[17] studied the penetration of fluorescein, in association with histamines, into the anterior chamber of the eye and came to much the same conclusion.

According to Wolfred,[18] the accepted hypothesis of the antihistamine drugs is that they attach themselves to the histamine receptors in the cells, blocking or preventing attachment of the histamines released by the antigen-antibody reaction. They also prevent capillary permeability and vasodilatation by blocking histamine, as evidenced by decreased erythema response. The antihistamine drugs by themselves have very little pharmacologic activity and in therapeutic doses do not significantly affect a normal organism. They produce their effect only under pathologic conditions where histamine is released. A solution of histamine is not destroyed nor is its action modified when mixed with antihistamine drugs *in vitro*. Manifestations of antihistamine toxicity, such as vertigo, drowsiness, headache or gastrointestinal irritation seldom necessitate the discontinuance of the drugs. Few blood dyscrasias and little tissue toxicity in therapeutic doses have been demonstrated, and cumulative, addictive properties have not been reported.

In December 1951, Kessler and Van Emburgh[5] reported a study of the use of antihistamine in the treatment of surgical and accidental trauma. They observed two groups of patients: (1) those exposed to accidental trauma in which there was a crushing injury and (2) those exposed to surgical trauma, for example, cholecystectomy, bowel resection and prostatectomy. The criteria for evaluating the success of treatment with antihistamines were control of pain, local tissue edema, tissue reaction around draining regions, serum oozing and the time factor in wound healing. The investigators used the evaluation of tissue edema and symptoms of pain as the two major criteria in recording their observations because of the ease of calibration.

One hundred cases of accidental trauma in which antihistamine therapy was used were studied, and another hundred cases in which no such therapy was instituted were reviewed as controls. The surgical trauma group was studied differently. Three sets of vials were set up and labeled as formulas A, B and C. Formula A contained antazoline hydrochloride (Antistine), 50 mg. per cubic centimeter, Formula B was a control and Formula C contained tripelennamine hydrochloride (Pyribenzamine), 25 mg. per cubic centimeter. One of the authors was not familiar with the contents and was told to make objective observations using the criteria cited above. Ninety-eight cases were included in this group. Kessler states in conclusion:

> On the basis of the criteria set up for evaluating the effectiveness of antihistamines in minimizing the effects of trauma, it was felt that these drugs have definite value. The observations indicate that pain is markedly decreased following their administration in both surgical and accidental trauma. Edema is markedly decreased by the administration of these drugs.

17. Halpern, B. N. A new synthetic antihistamine substance derived from phenothiazine. Canad. M. A. J. 59:322 Oct. 1948.

18. Wolfred, Morris M. Antihistamine drugs in dentistry. Am. J. Pharm. 123:13 Jan. 1951.

There is also a definite decrease in edema following surgical trauma, as evidenced by the absence of tissue reaction around the traumatized area. The effectiveness of the antihistamines in the cases studied indicates that histamine must play an important role in the phenomenon of trauma.

This concurs with many other reports in the literature as far as edema and tissue reaction are concerned; however, Kutscher and Chilton[19] using the Wolff-Hardy-Goodell technic for measuring pain threshold, reported only an insignificant rise in the pain threshold after the use of the two antihistamines.

The inception of the use of antihistamines in oral surgery came through the work of Silverman[1] which he reported to the American Society of Oral Surgeons on October 10, 1952. His work was carried out in much the same manner as Kessler's, with observation of the clinical results of administration of the same antihistamines, preoperatively and postoperatively. A report which he gave one year later to the same society verified his original beliefs.[20] Some of his observations were as follows:

1. The drugs have greatly improved the postoperative course following oral surgery.
2. Acute postoperative infection of wound areas attributable to surgical procedures rarely have been observed.
3. The great proportion of wounds have healed by first intention.
4. Secondary hemorrhage as a complication of surgery has not been seen during the use of these drugs.
5. Slough as a complication virtually has been eliminated.
6. There has been a tremendous reduction in the incidence of swelling. Where swelling does occur, resolution is much more rapid than formerly.
7. Trismus practically has ceased to be a complicating factor.
8. Independent of the sedative action of these drugs, the prevention of pain by their use has been successful.

Silverman also expressed the belief that the inherent characteristics of the barbiturates and the histamine release resulting from their use have been responsible for a great proportion of the postanesthetic complications observed in intravenous anesthesia. He feels that this situation has been reduced materially by the use of the antihistamine.

Maslansky,[3] by the use of injectable antihistamine (chlorprophenpyridamine maleate) with penicillin, obtained the same good clinical results. Buchanan[4] repeated the project with somewhat less satisfactory results. Again this study was a clinical observation and was aimed particularly at the edema factor involved.

■ *Materials and Methods*

The object of the following experiment was to find a technic by which the premise that antihistamine drugs in therapeutic dosage would shorten or benefit soft tissue healing after traumatic surgery might be verified. A standardized wound was inflicted on one flank each of a group of laboratory animals. These wounds were measured daily and the rate of healing was recorded. Two weeks later these same animals were wounded on the

19. Kutscher, H., and Chilton, N. W. Effect of antihistamines on the pain threshold: dolorimeter studies on pyribenzamine and antistine. Am. J. M. Sc. 223:239 March 1952.

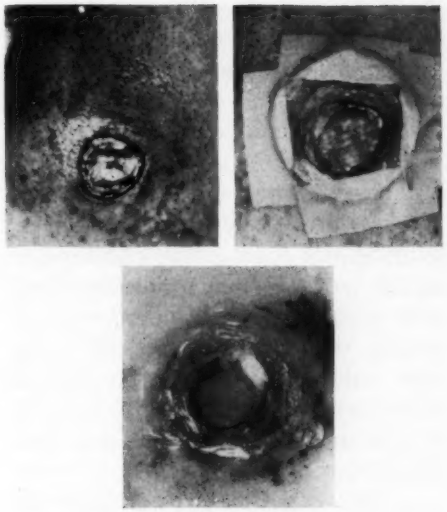
20. Silverman, R. E. Further clinical observations on the use of antihistamines in oral surgery. J. Oral Surg. 12:310 Oct. 1954.

opposite flank only after receiving both preoperative and postoperative varying dosage of an antihistamine. These wounds also were measured daily and their rate of healing was recorded. Thus a control was established. The experiment was designed to eliminate most of the variables, and the results were subjected to a statistical analysis.

A noninfected wound of normal skin heals rapidly by contraction, tissue growth and epithelization. With asepsis and protection of a standardized wound, healing time was found to be constant.[21] In the healing of a wound of the skin, the processes of contraction, growth of fibrous tissue and epithelization are grossly apparent. It is the impression of most workers that the process of epithelization usually is more sensitive and is more easily disturbed than the other two processes and that it needs care and protection. For this reason, a method used by Scheinberg, Bralow and Necheles[22] (in which the rate of wound healing by epithelization is measured and the factor of contraction is largely excluded) was modified.

At first a series of rabbits were used for the experiments; however, it was felt that this was impractical. Guinea pigs, therefore, became the laboratory animals. The data in this study concern the guinea pigs only.

Both male and female guinea pigs with an average weight of 250 Gm. were used. They were weighed before operation each day and every other day thereafter until the wounds were healed completely. On the day before the operation, the hair on their back and abdomen was clipped. A depilatory, sodium bisulfide,



Figure—Above left: Wound on guinea pig without protective covering on second postoperative day. Above right: Wound on guinea pig on fourth postoperative day. Below: Wound on rabbit flank viewed through transparent covering on fourth postoperative day. Note ingrowing epithelium

then was used. The animals were anesthetized intraperitoneally with a barbiturate, 20 mg. per kilogram of body weight. The skin was cleansed with soap and water followed by alcohol and ether. A wound approximately 1.0 cm. in diameter was made in the saddle area of the flank (illustration, above left). The skin of the circular wound was dissected out with scissors down to the subcutaneous layer, and little bleeding was encountered.

A polymerized methyl methacrylate (Lucite) ring then was glued tightly to

21. Carrel, A. Cicatrization of wounds. J. Exper. Med. 24:429 Nov. 1916.

22. Scheinberg, S.; Bralow, S. P., and Necheles, H. Experimental study of wound healing; new technique and study of effect of detergents and of antacid on wound healing. Surgery 24:972 Dec. 1948.

the skin surrounding the wound with a methacrylate polymer solution. The outside diameter of the ring was approximately 25 mm., the inner diameter was 14 mm. and the thickness of the ring was 1 mm. This ring aided in preventing wound contraction. The surface of the ring was covered by a transparent x-ray film that was cemented to it with methacrylate polymer solution. This film served as a window through which the rate of healing could be observed. The rings were reinforced with adhesive tape in order to protect them from damage by the animals and did not seem to disturb them (illustration, above right).

The wound areas were measured by placing a piece of celluloid on the surface of the window and tracing the line of union between epithelial edge and granulating surface. Since the window was only 1 to 2 mm. above the wound, and since the margins of the ingrowing epithelium could be distinguished easily (illustration, below), the outlines could be traced accurately.

The area of tracing was measured with a planimeter, according to the technic of Carrel.[21] Wound healing was expressed as the size of the healed area in per cent of the area of the original wound.

Tracing of the wounds was made daily on transparent x-ray film. A fine art pen and India ink were used. These tracings were enlarged four times by the use of photographic equipment. By the enlargement of the tracing, the use of the planimeter was facilitated and its accuracy was increased. For final results, the figures were reduced mathematically to the proportionate sizes.

Most reliance was placed on the proportion of animals showing 80 per cent of the wounds on the eighth day. Healing was definitely progressive on that date. Also, on comparison of the results, it became evident that on the eighth day, differences between the series of experimental animals were most pronounced.

The first consideration was the choice of antihistamine. It was desired to use only one drug. Since both Silverman[1, 20] and Ewing[23] had obtained encouraging results with the use of a compound of pyrrobutamine, which is the diphosphate of 1-p-chlorophenyl-2-phenyl-4-pyrrolidino-2-butene; methapyrilene hydrochloride and cyclopentamine hydrochloride (Co-Pyronil), and since experimental vials of injectable pyrrobutamine (Pyronil) were furnished,[24] it was decided that this antihistamine would be used.

DOSAGE—In determination of the proper dosage for a study such as this, influential factors such as age and weight were removed because of the standardization of the experimental animal. Of course, individual variation, an important factor in evaluating results, would be impossible to determine. Severity of the wound and trauma were standardized for all practical purposes, thus ruling these out as an influence in dictating proper doses.

It seemed logical to use as a base line the arbitrary dosages prescribed for man by Silverman,[1] Maslansky,[3] and so forth and to reduce these in a direct proportion as to weight. It was learned, later, that

23. Ewing, William T. Personal communication.

24. Experimental vials of injectable Pyronil were furnished by the Eli Lilly Company, Indianapolis.

this was a fallacy. Early dosages set up in this manner were wholly inadequate. Pyrrobutamine in its injectable form is at present available in concentration of 4, 6 and 10 mg. per cubic centimeter. The average man of 150 pounds is dispensed 15 mg. every four hours. To date, the optimum results with experimental animals have been obtained at a dose of 7 to 8 times that amount in proportion to body weight.

EXPERIMENT—Five animals were operated on at one time. No antihistamines were used, and the margin of the healing wound was traced daily for a period of ten days. The lesions served as a control. The same animals received standard wounds on the opposite flank two weeks later. To these animals antihistamines were dispensed as follows: 0.4 mg. intramuscularly, 30 to 60 minutes before surgical procedure and 0.8 mg. daily for the next four days. These wounds were also traced daily and the results were compared with the control series. Several series were run with varying dosages. Wounds with low-grade infections healed as well as clean, noninfected wounds. Animals with distinctly infected wounds were discarded. All animals were fed the same diet, a commercial brand of prepared rabbit food with lettuce. Wound healing in the controls and in the antihistamine animals was observed. Two animals not operated on but shaved, anesthetized, weighed and fed the same as the other animals were also observed. It was found that variations in body weight, red blood cells, hemoglobin and total proteins were insignificant.

On the third day of healing, the protective cover over the wound was removed from each animal. A small amount of the serous exudate was pipetted off, and the pH was determined.

■ *Results and Discussion*

The results of the experiment are given in the table.

In the control group, Group A, no antihistamines were used. There was no consistency in the rate of healing until about the sixth or seventh day. During this time there was an extreme range, from minus figures, as a result of wound expansion, up to 55 per cent healing. On about the sixth postoperative day, the healing developed into an orderly maturation and division of cells, and sequential results began to appear. The eighth day was the first on which 100 per cent healing was seen. The average time for complete healing of all the wounds was 11.3 days. Because of the inaccuracy of interpreting complete healing, the mean for 50 per cent healing also was recorded for all the groups. This was done to facilitate statistical studies. The mean for 50 per cent healing for the 20 wounds in the control was 8.22 days.

In Group B, pyrrobutamine (0.2 mg.) was injected intramuscularly 60 minutes preoperatively. A dose of 0.4 mg. was injected daily for the next four days. The first complete healing was recorded on the ninth postoperative day, and the average number of days for 100 per cent healing was 10.2. The 50 per cent healing mean was 8.06 days.

The dose was increased in Group C. Pyrrobutamine (0.4 mg.) was injected preoperatively and 0.8 mg. daily for the next four days. There was a noticeable

Table

Average percentage rate of healing with varying dosages of pyrrobutamine

Group	No. wounds	Dosage		Postoperative days									Av. days 50% healing	Av. days 100% healing
				1	6	7	8	9	10	11	12	13		
A	20	Control	Av. % healing	10.2	24.0	35.7	52.0	71.0	77.9	91.0	99.0	100.0	8.2	11.3
			No. completely healed	0	0	0	1	1	2	4	10	2		
B	10	Pyrrobutamine, 0.2 mg. preop. 0.4 mg. daily	Av. % healing	4.0	28.0	33.0	59.0	61.0	71.0	92.0	100.0		8.0	10.2
			No. completely healed	0	0	0	0	2	5	2	1			
C	10	Pyrrobutamine, 0.4 mg. preop. 0.8 mg. daily	Av. % healing	8.7	66.0	84.5	94.2	100.0					5.2	8.5
			No. completely healed	0	0	0	5	5						
D	10	Pyrrobutamine, 0.6 mg. preop. 1.0 mg. daily	Av. % healing	4.3	67.0	73.0	80.9	98.2	100.0				5.7	9.1
			No. completely healed	0	0	0	2	5	3					
E	8	Pyrrobutamine, postop. only 0.8 mg. daily	Av. % healing	5.3	37.1	46.9	65.1	76.8	88.7	96.8	100.0		8.6	11.125
			No. completely healed	0	0	0	0	0	2	3	3			

improvement in healing time. All ten wounds were healed by the ninth postoperative day. The average number of days for complete healing was 8.5 days, 2.8 days less than the control group. The 50 per cent mean was 5.21 days.

The dose in Group D was increased still further over Group C. Pyrrobutamine (0.6 mg.) was injected preoperatively and 1.0 mg. daily for the next four days. The mean time for 100 per cent healing was 9.1 days. Fifty per cent healing required an average of 5.69 days. Apparently, the optimum dose is between those administered to Groups C and D. It is possible that an overdose was given and the healing actually was retarded.

Group E was given 0.8 mg. pyrrobutamine postoperatively only; the premedication was omitted. The results paralleled those of the control. A mean of 11.125 days was required for 100 per cent healing, and a 50 per cent healing occurred in 8.57 days.

The pH determinations on the third day of healing were as follows:

1. Control A, 5.8 to 7.2.
2. Group B, 6.9 to 7.5.
3. Group C, 7.1 to 8.1.

4. Group D, 6.8 to 7.8.
5. Group E, 6.9 to 7.4.

The results of the experiment were subjected to a statistical significance evaluation.[25] The validity of the antihistamine effect in Groups C and D has been upheld statistically; the results for Group B and E are not conclusive.

Obviously, Group C had a near optimum dosage as is shown by the fact that it had the shortest healing time, if it is assumed that antihistamines are a factor. Group D was probably overdosed. This statement is based on the increased healing time and the day to day appearance of the animals. They were less aggressive than the rest and appeared to be under the influence of a hypnotic. Possibly their metabolism was slowed with a resultant lower wound healing time.

It appears that the importance of attaining an adequate preoperative blood level was demonstrated in Group E. Without the injection of the antihistamine before surgery but with daily injections, the same as in Group C, the healing time rose to a level approaching that of the control.

Hartwell[26] stated that epithelization takes place through ameboid movement into the wound of the epithelial cells from the surrounding epithelium. Epithelization is completed by union of extension membranes growing from the edges of the wound. According to Hartwell,[26] the formation of such membranes is dependent on the presence of a supporting base suitable for epithelial cell movement. The base is a factor in the support, advancement and ultimate union of the epithelial outgrowth from the edges of a wound. The presence of an unsuitable base is probably one of the causes of delayed wound healing, and it may be responsible in part for the formation of indolent wounds.

Another factor in wound healing is pH. Heterolysis seems to depend mainly on action of leukocytic enzymes which, in an alkaline environment, digest dead tissue but which do not attack living cells or unchanged connective tissue fibers. This heterolysis of dead tissue permits the removal of barriers to the extension membranes and allows for the ameboid activity of the epithelial cell. Masser and McClellan[27] found that wounds benefited more from an alkaline pH than from an acid pH. Our findings seemed to corroborate this fact, for those wounds on the antihistamine animals showed a definite trend toward alkalinity, the range of pH being from 6.9 to 8.1, whereas the pH of the control animals ran from 5.8 to 7.2. Goodman[28] stated that most investigators agree that histamine acts much more intensely on acid-producing cells of the body.

The effect of antihistamine on local inflammation and edema has been investigated by various other workers but only at a clinical level. Mayer[29] and his group have pointed out that inflamed tissue has a higher hyaluronidase content than normal tissue, and that tripelennamine (Pyribenzamine) and antazoline hydrochloride (Antistine) have the capacity either

25. Snedecor, George W. Statistical methods applied to experiments in agriculture and biology. Dubuque, Iowa, William C. Brown Co., 1950.

26. Hartwell, S. W. Various parietal tissues in healing of surgical wounds: healing of epithelium. Proc. Staff. Meet., Mayo Clinic 3:244 Nov. 28, 1928.

27. Masser, F. C., and McClellan, R. H. Surgical maggots: study of their functions in wound healing. J. Lab. & Clin. Med. 20:1219 Sept. 1935.

28. Goodman, Louis, and Gilman, Alfred. Pharmacological basis of therapeutics. New York, Macmillan Co., 1941, p. 569.

29. Mayer, R. L. Hyaluronidase and inflammation of skin. Ann. New York Acad. Sc. 52:1041 May 31, 1950.

to destroy or to limit the action of hyaluronidase, which is known as the spreading factor. This would explain the localization of inflammatory processes in accidental and surgical trauma after the administration of these preparations.

It is felt that an experimental confirmation of the therapeutic efficacy of antihistamine in the control of edema after surgical manipulation would be desirable. An approach to this problem is suggested by the work of Finnegan and others,[30] utilizing the comparative wet and dry weights of the rabbit eyelids, one eyelid being traumatized in a standardized manner, the other untreated.

■ SUMMARY AND CONCLUSIONS

A method for the study of wound healing is offered in an attempt to determine the effects of an antihistamine on the healing rate of soft tissue. The method involves the infliction of a standardized cutaneous defect in the flank of the guinea pig.

On the basis of the experimental results described herein, the following conclusions are drawn:

1. An injectable antihistamine, pyrrobutamine, produces a significant increase in the rate of wound healing.
2. There appears to be an optimum dose in the guinea pig for beneficial effects on wound healing.
3. Preoperative, as well as postoperative, administration of the antihistamine appears to be necessary to attain the maximum increase in the rate of wound healing.

30. Finnegan, J. K., and others. Quantitative method for measurement of cigarette smoke irritation. J. Pharmacol. & Exper. Therap. 89:115 Feb. 1947.

■ Progress of Science

In the progress of science there are two processes at work. In the one there is the steady accumulation of factual knowledge, and in the other there is an attempt to interpret the facts in terms of unifying principles. It is the interplay of theory and experiment which leads to the most important advances, for often the interpretation of one sort of fact leads to the prediction of new results. The most impressive advances are produced when general hypotheses are put forward which bring different branches of science within the same comprehensive scheme. *John Lennard-Jones, "New Ideas in Chemistry," Scientific Monthly 80:175 March 1955.*

Chemical determination of histamine content of oral tissues and saliva

■ *Samuel G. Sanders, D.D.S., M.S., Jackson, Miss.*

Fundamental data regarding the histamine content of the oral tissues and of saliva are lacking. Saliva forms a large segment of the environment of oral surgical wounds and has been found to contain histamine in significant quantities.[1,2] Information about the histamine content of the oral tissues and saliva, therefore, is important if the possible value of antihistamines in oral surgery is considered.

■ *Method of Study*

The methods that previously have been in use for the estimation of small quantities of histamine have been based on bio-assay with strips of guinea pig ileum. Such methods are not extremely accurate or sensitive and are fraught with sources of possible interference and error. A direct chemical method, therefore, would be more desirable.

A report by Sanger[3] in 1945 that dinitrofluorobenzene is a suitable reagent for the amino group, suggested to Lowery and co-workers[4] and McIntire, White and Sproull[5] that under certain controlled conditions of pH, time, temperature and concentrations, histamine and dinitrofluorobenzene would react to give a maximum yield of a water soluble yellow derivative suitable for spectrophotometric use.

Lowery and his co-workers[4] subsequently developed a method of chemical determination of histamine which is accurate to within a 10 per cent margin of error when concentrations of 0.1 or more micrograms of histamine are used. This procedure, with a few minor adaptations, was utilized in this study.

The five essential steps are:

1. Extraction of the histamine from biologic material with trichloracetic acid.

2. Concentration of the histamine and separation from many other amines by absorption onto an exchange silicate (Decalso) in a specially prepared Decalso column (Fig. 1), then elution with 40 per cent potassium bromide.

3. Formation of the colored derivative of histamine with dinitrofluorobenzene.

4. Further concentration and separation of the histamine derivative from dinitrofluorobenzene derivatives of remaining amines by extraction into methyl-n-hexyl ketone (2,-octanone), followed by extraction into a small amount of hydrochloric acid.

Condensation of a thesis submitted to the graduate committee of the Washington University School of Dentistry, St. Louis, in partial fulfillment of the requirements for the degree of Master of Science in oral surgery.

1. Riesser, Otto. Histaminstudien. Arch. f. exper. Path. u. Pharmakol. 187:1, 1937.

2. Ungar, G., and Pocoule, A. Sur les voies d'elimination de l'histamine et son absence dans les urines normales. Compt. rend. Soc. de biol. 124:1204, 1937.

3. Sanger, F. Free amino groups of insulin. Biochem. J. 39:507, 1945.

4. Lowery, O. H., and others. Chemical measurement of histamine in blood plasma and cells. Unpublished.

5. McIntire, F. C.; White, F. B., and Sproull, M. Determination of histamine with 2, 4-dinitrofluorobenzene. Arch. Biochem. 29:376 Dec. 1950.

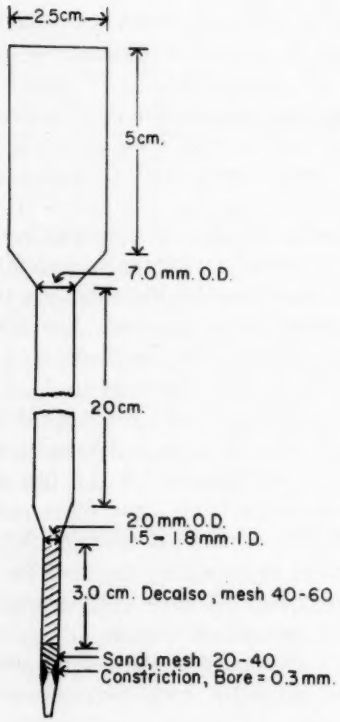


Fig. 1—Decalso column for histamine absorption. O.D., outside diameter. I.D., inside diameter

5. Spectrophotometric measurement of the color of the acid solutions in a Model DU Beckman spectrophotometer adapted to give readings with a minimum sample of 25 to 35 microliters through a red filter and a 1.8 mm. slit opening at a wave length of 360 millimicrons. Comparison of known standards to unknown give a basis for quantitative computations.

■ *Histamine Content*

HUMAN GINGIVA—Samples of apparently normal, freshly excised human gingiva from three subjects were collected and placed in tightly sealed, previously weighed, silicone-treated test tubes. These tubes with their contents were reweighed, and the differences between the two weights were taken as the wet weight of the specimens. The specimens were then chemically analyzed for histamine content. The results in micrograms of histamine per gram of tissue were 5.21, 6.66 and 7.78. The mean was 6.55 micrograms per gram. This value was close to that of skin as determined by Graham.[6]

NORMAL HUMAN SALIVA—Expectorated saliva samples were collected in silicone-treated tubes from 24 subjects without known injury, infection, or allergy. These samples were collected at least three hours after feedings and brushing of the teeth. Expectorated saliva was used because of the interest in the environment of the oral surgical wound. These 48 samples then were analyzed for histamine content and found to contain from 106.5 to 181.0 micrograms of histamine per liter of saliva, with a mean of 145.6 micrograms.

SALIVA AFTER ANTIHISTAMINE—Samples of expectorated saliva were collected at 24 hour intervals from six subjects with no known injury, infection, or allergy. For the 24 hour periods preceding the third and fourth sample collections, the subjects received orally either pyrrobutamine, which is the diphosphate salt of 1-p-chlorophenyl-2-phenyl-4-pyrrolidino-2-butene (Pyronil), 15 mg., or a compound of pyrrobutamine, methapyrilene hydro-

6. Graham, Helen T. Personal communication, April 1954.

chloride and cyclopentamine hydrochloride (Co-Pyronil), 52.5 mg. every four hours. Three of the subjects received each. These antihistamine compounds were selected for use because they were used by Silverman[7] in his initial work and were reported to be of therapeutic value.[8,9]

The first 24 hours of antihistamine therapy reduced the mean histamine content of the pretherapeutic saliva from 141.6 to 91.5 micrograms per liter, a mean reduction of 50.1 micrograms per liter.

The second 24 hours of antihistamine therapy reduced the pretherapeutic mean from 141.6 to 76.3 micrograms per liter, a mean reduction of 65.3.

The first 24 hours after the cessation of antihistamine therapy, a continued but lessened reduction of the pretherapeutic mean from 141.6 to 119.2 micrograms per liter was noted. A mean reduction of 22.4, therefore, resulted.

The second 24 hours after the cessation of antihistamine therapy, the level of the mean histamine content of the saliva was almost up to the level of the pretherapeutic normal mean.

When subjected to statistical analysis to rule out the possibility of chance, these data were found to be highly significant statistically.

SALIVA AND SURGICAL PROCEDURE—Seven patients who had traumatic intraoral surgical procedures were studied. All the operations performed were similar in regard to trauma and extent, and all included the reflection of soft tissue and surgical trauma to the alveolar bone. Samples of expectorated saliva were collected at 24 hour intervals for five days and were analyzed for histamine content. The surgical procedures were performed shortly after the collection of the second samples. Six of the patients were hospital inpatients who received general anesthetics; one was an outpatient anesthetized with a mandibular nerve block with 1.5 cc. of 2 per cent lidocaine hydrochloride. No other drugs were administered except necessary analgesics and sedatives.

The first 24 hour postoperative period showed an increase over the preoperative mean histamine content from 169.4 micrograms per liter to 668.9, a mean increase of 499.5.

The second 24 hour postoperative period showed a continued but lessened increase over the preoperative mean content from 169.4 to 388.0 micrograms per liter, a mean increase of 218.6.

The third 24 hour postoperative period showed the mean to be 221.8 micrograms per liter, an increase in the preoperative mean (169.4) of only 52.4. These salivary histamine increases were found to be highly significant statistically.

SALIVA BEFORE AND AFTER SURGERY AND ANTIHISTAMINE THERAPY—Seven patients who had traumatic intraoral surgical procedures were studied. These operations also were similar in regard to trauma and extent, and all included the reflection of soft tissue and surgical trauma to the alveolar bone.

Samples of expectorated saliva were

7. Silverman, R. E. Use of antihistamines in oral surgery; preliminary report. J. Oral Surg. 11:231 July 1953.
8. Mothersill, M. H. Prolonged antihistamine action. J. Indiana M. A. 45:786 Aug. 1952.
9. Lee, H. M.; Anderson, R. C., and Harris, P. N. Antihistaminic action of "pyronil". Proc. Soc. Exper. Biol. & Med. 80:458 July 1952.

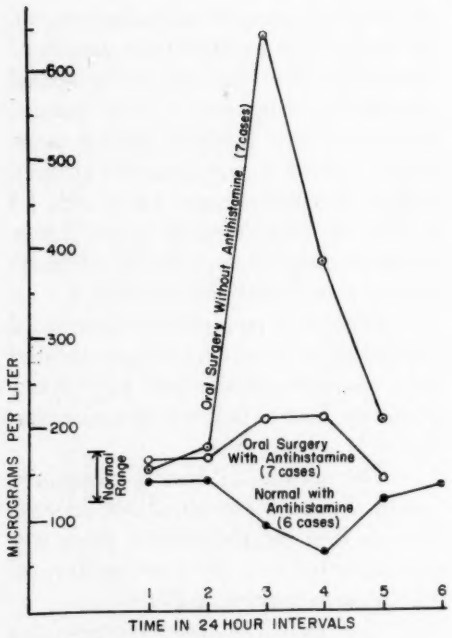


Fig. 2—Daily mean histamine content of human saliva of three groups of patients: (1) those receiving antihistamine, (2) those having traumatic, oral surgical procedures and (3) those having traumatic oral surgical procedures with accompanying antihistamine therapy

collected at 24 hour intervals for five days and were analyzed for histamine content. Shortly after the second samples were collected, antihistamine therapy of pyrrobutamine, 15 mg., or pyrrobutamine compound, 52.5 mg., every four hours for three days, was initiated; four of the patients received pyrrobutamine compound, and the other three received pyrrobutamine. All seven patients were hospitalized and received general anesthetics. The surgical procedures were done shortly after the initial antihistamine medication. No other drugs were administered to the patients except necessary analgesics and sedatives.

The first 24 hour postoperative period showed an increase in the normal histamine content from 168.2 to 216.5 micrograms per liter, a mean increase of 48.3.

The second 24 hour postoperative period showed an increase in the mean normal histamine content from 168.2 to 206.1 micrograms per liter, a mean increase of 37.9.

The third 24 hour postoperative period showed a decrease in the mean normal histamine content from 168.2 to 150.9 micrograms per liter, a mean decrease of 17.3.

Statistical analysis of these data shows a low statistical significance and a high probability of chance error in the small deviations from the mean normal values of this group. The wide range of the determinations reduces their significance.

The principal point here, however, is not the significance of the small deviations of the histamine content of the saliva of these patients from their mean preoperative value but the fact that this deviation is small compared to the great increase in histamine in those surgical patients not receiving antihistamine therapy in the preceding group studied. This difference was found to be of high statistical significance. The over-all results are shown graphically in Figure 2.

■ *Discussion*

The results reported herein show a significant level of histamine in the saliva without wide daily variation in the normal person. The mean histamine content of saliva of 145.6 micrograms per liter is only

slightly higher than that reported by other investigators using bio-assay technics. It is close to the 122.0 micrograms reported by Graham[10] for whole blood. Unfortunately, the lack of 30 ml. daily blood samples prevented a parallel study. The cellular contents of the saliva were not counted, though such a study might have proved interesting inasmuch as Wright and Jenkins[11] found numerous leukocytes in the saliva, both intact and in various stages of destruction. Such cells, of course, constitute another source of histamine in the saliva. In the laboratory experiments reported here, however, there seemed to be little correlation between the histamine content of the postoperative saliva specimens and their visible bloodiness, unless the amount of blood was extreme, in which case high saliva histamine content was noted.

The destruction of tissue cells, leukocytes and protein food debris, and the action of oral bacteria are not to be ignored as potential sources of salivary histamine. Ackermann[12] produced histamine by histidine putrefaction. The work of Knott and Oriel[13] and others[14,15] demonstrates that histamine can be produced by the action of microbes. Kirch and his co-workers[16] found histidine in saliva in the significant range of 0.35 to 2.0 mg. per 100 ml.

Evidence that certain free volatile amines appear in the saliva in greater quantity with destructive gingival and periodontal disease might indicate that histamine is also produced by tissue lysis.[17] In my experiment the two groups of patients who had poorer oral hygiene and much more gingival and periodontal disease than the normal group had the higher amounts of histamine in their saliva.

A sharp increase in salivary histamine was demonstrated after oral surgical procedures. The amount of histamine returns to a nearly normal value by the third postoperative day. The possible sources of salivary histamine have been discussed; undoubtedly the additional amount of histamine seen after trauma is from similar sources. Trauma to soft tissues and bone marrow (both rich in histamine) as well as the release of blood and tissue fluids could all be cited as possible sources of local histamine release, as well as possible increased tissue lysis and microbial activity. Whether or not a more generalized reaction takes place was not determined. It has been shown that a rise in blood histamine activity follows trauma.[18,19] Craver[20] cites some experimental evidence that histamine is well absorbed from the oral cavity and that lingual doses have proved lethal to guinea pigs. Certainly the trauma associated with

10. Graham, Helen T., and others. Distribution of histamine among blood elements. (Abst.) Fed. Proc. 11:350 March 1952.

11. Wright, D. E., and Jenkins, G. N. Leukocytes in the saliva of caries-free and caries-active subjects. J. D. Res. 32:511 Aug. 1953.

12. Ackermann, D. Uber den bakteriellen Abbau des Histidins. Zeitschr. f. physiol. Chem. 65:504, 1910.

13. Knott, F. A., and Oriel, G. H. Detection of histamine-like substances in asthmatic sputa and experiments on their possible bacteriological origin. Proceedings of Physiological Society. J. Physiol. 70:xxxi, 1930.

14. Kleiner, I. S. Human biochemistry. St. Louis, The C. V. Mosby Co., 1945, p. 312.

15. Best, C. H., and Taylor, N. B. Physiological basis of medical practice, ed. 5. Baltimore, Williams and Wilkins Co., 1950, p. 294, 295, 318 and 526.

16. Kirch, E. R., and others. Amino acids in human saliva. J. D. Res. 26:297 Aug. 1947.

17. Fosdick, L. S.; Blackwell, R. Q., and Carter, W. J. Chemical studies in periodontal disease. J. D. Res. 32:646 Oct. 1953.

18. Dale, H. H. Antihistaminic agents in allergy; pharmacology of histamines. Ann. New York Acad. Sc. 50:1017 April 28, 1950.

19. Leonard, Frederick, and Huttrer, C. P. Histamine antagonists. Washington, D. C., National Research Council, Chemical-Biological Coordination Center, Review no. 3, 1950, p. 1-40.

20. Craver, B. N. Antihistamine agents in allergy; pharmacodynamics of histamine. Ann. New York Acad. Sc. 50:1029 April 28, 1950.

surgery, either oral or extraoral, with its accompanying histamine release must elicit some systemic reactions which possibly could include histamine liberation from more distant sites. The stimulating effect on salivary secretion exerted by activated histamine might in some manner increase the salivary histamine content. The chemical method of histamine determination used gives only the total histamine content. This method cannot differentiate between the free, or active, and the bound, or inactive, forms of histamine.

The depression of salivary histamine content by pyrrobutamine therapy is difficult to account for in light of the best accepted theory of antihistamine action, which is that antihistamines antagonize histamine at the site of action without destroying it or preventing its release. If such is the case one must look elsewhere for reasons for this depression among the other effects antihistamines exert.

Perhaps the depression of salivation or the antimicrobial effect by these compounds[21,22] may inhibit histamine production in the saliva. Possibly the antihistamines influence the secretory cells of the salivary glands and thereby inhibit the formation or secretion of histamine.

The laboratory work in this study was done on expectorated or free saliva from the mouth because it makes up the outside environment for oral surgery wounds. The study of the histamine content of cannulated as well as free saliva samples with parallel blood samples under the conditions imposed in this study would provide valuable information in both extraoral and intraoral surgery. Certainly a more closely observed clinical study in which neither patient nor observer knew what medication was being given and in which a larger group of patients was used would be of value.

■ *Conclusions*

The histamine content of gingival tissue and free saliva under conditions of antihistamine therapy, oral surgery and oral surgery with concurrent antihistamine therapy was determined by microchemical analysis. A clinical observation study of the patients used in the laboratory investigations and others under similar conditions was made.

On the basis of the data and observations presented herein the following conclusions may be drawn:

1. Histamine is present in human gingival tissue in quantities similar to that found in skin.

2. Histamine is present in free human saliva in significant quantities without wide daily variations in the normal state.

3. The histamine level in free human saliva is sharply and significantly elevated for two or three days or more following intraoral surgery.

4. The histamine level in free human saliva is depressed by administration of pyrrobutamine, an antihistamine.

5. The histamine level in expectorated human saliva after intraoral surgical

21. Hagerman, G., and Nilzen, A. Antihistamine studies with bacteriologic technique. Acta Dermat.-Venereol. 32:364, 1952.

22. Stewart, G. G. Antimicrobial activity of four antihistamine compounds. Oral Surg., Oral Med. & Oral Path. 5:1000 Sept. 1952.

procedures is significantly less in those patients receiving pyrrobutamine than in those not receiving antihistamine therapy.

6. Antihistamines seem to have definite value in the postoperative course of certain patients who had required oral surgical procedures. Further investigation is needed regarding the antihistamine agent of choice, the dosage and the exact mechanism of the beneficial action or actions.—*Lamar Life Building.*

The safety of anesthesia in the dental office

■ *Harry M. Seldin, D.D.S., New York, and Benjamin S. Recant, D.D.S., Long Island City, N. Y.*

Deaths directly attributable to the use of anesthetics, regional or general, have been reported since the origin of the use of such drugs.[1] The employment of any anesthetic is accompanied by the danger of possible loss of life. This is true when any anesthetic drug is administered, whether it is for medical, surgical or dental procedures.

Periodically, highly publicized reports of a dental anesthetic fatality appear in the press. Such reports present a picture completely out of proportion to the frequency of such fatalities. Even competent medical anesthesiologists occasionally have voiced criticism of the dental use of anesthetics, basing their criticism on the supposed frequency of such fatalities.[2]

The authors decided, therefore, to determine the mortality rate directly attributable to an anesthetic in ambulatory patients undergoing anesthesia in dental offices for dental procedures, in order to determine the safety of this kind of anesthesia. In addition it was decided to compare the frequency of deaths occurring in the dental office with those resulting from the administration of anesthesia in hospitals and medical offices by physicians or approved nurse anesthetists, that is, supervised to a greater or lesser degree by trained medical anesthesiologists.

It was decided to use for this study only those anesthetic deaths in which anesthesia had been administered for procedures of approximately similar severity or duration to those in the dental office, and to those patients whose medical status might be assumed to have been similar to

1. Beecher, H. K. First anesthesia death with some remarks suggested by it on fields of laboratory and clinic in appraisal of new anesthetic agents. Anesthesiology 2:443 July 1941.

2. Barach, A. L., and Rovenstine, E. H. Hazard of anoxia during nitrous oxide anesthesia. Anesthesiology 6:449 Sept. 1945.

that of patients whom the dentist confronts in his daily practice. Most minor otorhinolaryngological and ophthalmological procedures are in this category.

Accurate statistics on anesthetic deaths unfortunately are extremely difficult to obtain. It is often impossible to determine accurately the role played by an anesthetic in the production of a fatality. As Clement[3] states:

> In many instances anesthesia has been unjustly blamed for a fatal outcome; in other instances the anesthesia had doubtless been responsible for death occurring perhaps hours after the patient has left the operating room. Fatalities, if reported at all, are usually done so reluctantly; morbidity figures are too frequently inaccurate.

Waters and Gillespie[4] write:

> When a patient dies during an operation several factors must be carefully considered in assigning the cause of death. These are: the condition of the patient, the nature of the operation and the skill with which it was performed, the agent and technique of anesthesia, the wisdom and skill with which they were used, and the degree of clinical acumen displayed by the surgeon and anesthetist in treating the condition when it was recognized that an emergency had arisen. In the majority of cases a combination of these factors has been responsible for the fatal outcome, and it is impossible to assign the responsibility exactly.

In many hospitals the determination of whether a fatality was due primarily to the anesthesia or to the surgical procedure often depends on the measure of dominance of the anesthetist or the surgeon at the mortality conference.

It was found after investigation that one of the more reliable sources available for examination of mortality statistics was the files of the office of the chief medical examiner of the city of New York. In the city of New York all deaths, regardless of cause, must be reported to this office. The mortality files are classified according to cause of death as determined by death certificate, hospital report and autopsy, when available. A study of these records presented an over-all picture of anesthetic deaths in the city of New York.

The study was limited to statistics for the ten year period 1943 through 1952, which is a sufficiently long period of time to minimize statistical error. It also offers an opportunity to examine on a statistical level the progress that is being made in the prevention of dental anesthetic deaths. Of course, the study of these records does not preclude the previously mentioned error of improper or inaccurate determination of whether death was due primarily to the anesthesia or to the surgical procedure. No such possibility of error regarding anesthetic deaths in the dental office, however, existed. These deaths hardly could have been reported as surgical deaths. Similarly, limiting the comparison of dental anesthetic deaths with deaths in which the anesthetic was used for relatively minor surgery, such as tonsillectomy, also limits the possibility of error in the determination of the cause of death, thus making the comparison more worthwhile.

■ *Data*

Table 1 reveals a low percentage of dental anesthetic deaths in the city of New York in the ten year period of this study. It was extremely difficult to com-

3. Clement, F. W. Nitrous oxide-oxygen anesthesia. Anesthesiology 7:616 Nov. 1946.

4. Waters, R. M., and Gillespie, M. A. Deaths in operating room. Anesthesiology 5:113 March 1944.

Table 1

Anesthetic deaths

	1943	1944	1945*	1946	1947	1948	1949	1950	1951	1952	10 yr. total	Mean per cent 10 yr. total
Total anesthetic deaths†	145	173	81	176	205	238	238	239	206	166	1,867	
Total deaths (anesthesia in dental office)	2	2	1	0	2	0	1	0	0	0	8‡	0.43
Minimum deaths (anesthesia for tonsillectomy, adenoidectomy or both)	2	8	7	3	7	8	7	2	4	3	51§	2.7
Minimum deaths (anesthesia for ophthalmological procedures)	3	1	1	1	2	1	2	2	1	1	15	0.80

*Numbers for 1945 are incomplete (representing about one-half of total anesthetic deaths for 1945) because of incomplete filing and classification at office of chief medical examiner.

†Includes general, spinal and regional anesthesia.

‡Two additional anesthetic deaths in which anesthetic was administered in hospitals not included.

§Represents anesthetic deaths for tonsillectomies and adenoidectomies. Total number of anesthetic deaths for all otorhinolaryngological procedures is proportionately higher, as is percentage of deaths.

plete Table 1 with the total number of administrations of anesthesia for dental purposes in New York city and the total number for otolaryngology, ophthalmology and so forth. The tremendous number of administrations of anesthesia in dental offices, however, must be considered. Using a rather conservative figure of two injections by each dentist for each practice day, Nevin[5] in 1938 estimated that dentists throughout the United States and Canada make 35,000,000 injections of local anesthetics each year. There are at present approximately 9,000 dentists in the city of New York. It can be estimated with extreme conservatism that today the average dentist makes at least five administrations of local anesthesia in each practice day. If an average of 200 working days is assumed, the figure of 9,000,000 administrations of local anesthesia in New York city dental offices each year is reached. Dick's[6] estimate of 30,000,000 injections of local anesthetics yearly by all dentists appears to be considerably low. Thus 90,000,000 represents the number of administrations of local anesthesia in dental offices during the ten year period included in the present study.

In addition to the administrations of local anesthesia, it may be estimated conservatively that over 100,000 administrations of general anesthesia are made in New York city dental offices each year, that is, 1,000,000 in this ten year period. The total number of administrations of dental anesthesia is tremendously greater than any estimate of the total number of administrations of anesthesia for tonsillectomies and adenoidectomies or for

5. Nevin, M. 35,000,000 guinea pigs. D. Items Interest 60:685 July 1938.

6. Dick, S. P. Clinical toxicity of epinephrine anesthesia. Oral Surg., Oral Med. & Oral Path. 6:724 June 1953.

ophthalmological procedures. Despite this, the number of dental anesthetic deaths is lower than that of deaths due to the use of anesthetics for otorhinolaryngological or ophthalmological procedures (Tables 1 and 2).

The question of the anesthetic that had been used in the instances in which anesthetic fatalities had occurred deserves some study. From Table 3, it can be seen that there were two anesthetic deaths in which a local anesthetic, procaine hydrochloride, was used and six in which a general anesthetic, nitrous oxide-oxygen, was used. If the fact that many more local anesthetics are given than general is considered, it can be seen that percentage-wise, the local anesthetic safety record surpasses even the excellent record of general anesthetics in dentistry.

These results compare favorably with a study made by Nevin[5] of the coroner's records of the city of New York for the years 1936 and 1937. In both these years there were two deaths associated with the use of local anesthetics in dental offices, whereas in each year there were three deaths with nitrous oxide-oxygen and in 1937 one death with hexobarbital sodium (Evipal Sodium).

■ *Local Anesthetics*

The use of local anesthetics must not be considered to be without danger.

Table 2

Local anesthetic deaths in medicine and dentistry
Comparison of published statistics

Reporter	Total cases	Procedures	Anesthetic	Anesthetic deaths	Mean mortality percentage
Furstenberg and others[1]	30,000	Tonsillectomies	Cocaine hydrochloride	3	0.010
Ireland, Ferguson and Stark[2]	39,298	Ear, nose and throat	Cocaine hydrochloride & tetracaine hydrochloride	7	0.018
Schindler[3]	22,351	Gastroscopy	Cocaine hydrochloride & tetracaine hydrochloride	3	0.013
Williams[3]	6,378	Nose and throat	Cocaine hydrochloride	2	0.031
Seldin and Recant	90,000,000*	All dental procedures	Local anesthetics (mainly, procaine hydrochloride)	2	0.000002

*Based on estimated number of injections. If estimate is considered too high and it is divided in half (45,000,000 injections), a mean mortality percentage of 0.000004, still below that of any other study, is obtained.

†This would presumably include butethamine hydrochloride (Monocaine Hydrochloride), lidocaine hydrochloride (Xylocaine Hydrochloride), tetracaine hydrochloride (Pontocaine Hydrochloride) and so forth.

1. Furstenberg, A. C., and others. Evaluation of cocaine anesthesia: perpetuation of the equivocal concepts. Tr. Am. Acad. Ophth. 55:643 July-Aug. 1951.

2. Ireland, P. E., Ferguson, J. M. W., and Stark, E. J. Clinical and experimental comparison of cocaine and Pontocaine as topical anesthetics in otolaryngological practice. Laryngoscope 61:767 Aug. 1951.

3. Schindler, R. Results of questionnaire on fatalities in gastroscopy. Am. J. Digest. Dis. 7:293 July 1940.

Table 3
Anesthetics in dental office deaths

	1943	1944	1945	1946	1947	1948	1949	1950	1951	1952	10 yr. total
Procaine local	0	1	0	0	1	0	0	0	0	0	2
Nitrous oxide	2	1*	1	0	1	0	1	0	0	0	6
Intravenous barbiturate†	0	0	0	0	0	0	0	0	0	0	0
Total anesthetic deaths	2	2	1	0	2	0	1	0	0	0	8

*Intravenous hexobarbital sodium (Evipal Sodium) had also been used, but nitrous oxide-oxygen was listed as responsible agent. Barbiturates were found on autopsy.

†Two hospital anesthetic deaths in which anesthetic was administered for dental surgery are not included.

Periodically the literature produces case records of fatalities associated with the use of local anesthetics. The introduction and sufficient use of each new local anesthetic drug invariably is followed by reports of fatality accompanying its use. This was true for cocaine, introduced in 1884; procaine, in 1905; dibucaine hydrochloride (Nupercaine Hydrochloride), in 1925 and tetracaine hydrochloride (Pontocaine Hydrochloride), in 1933. It is already true for lidocaine hydrochloride (Xylocaine Hydrochloride),[7-9] introduced in 1948, despite its relatively excellent over-all safety record.

In 1924, the committee for the study of toxic effects of local anesthesia of the American Medical Association, established because of the reported frequency of toxic reactions with local anesthetics, reported 43 deaths.[10] In 1928 a further report by the Committee listed 14 additional deaths.[11] The commission appointed by the Philadelphia Medical Society reported 29 fatalities due to local anesthetics in the Philadelphia area from 1935 to 1946.[12] Waters and Gillespie,[4] reporting on 43,048 hospital administrations of anesthesia found six deaths in 4,835 injections of local anesthetics. Dealy[13] reporting on anesthetic fatalities at Queens General Hospital in New York city found five operating room fatalities with local anesthesia during the five year period January 1936 to January 1941. Lefkowitz[14] reporting on a study of the records of the office of the chief medical examiner of the city of New York for the 11 years from 1928 to 1939, found eight deaths which, after careful study and evaluation, could be ascribed to the use of a local anesthetic. Criep[15] recently reported on three deaths within one year due to allergic reactions to procaine.

In evaluating an anesthetic death in

7. Death after Xylocaine injection. Brit. M. J. 1:280 Feb. 2, 1952.

8. Hunter, A. R. Toxicity of Xylocaine. Brit. J. Anaesth. 23:153 July 1951.

9. Hanson, I. R., and Hingson, R. A. Use of Xylocaine, new local anesthetic, in surgery, obstetrics and therapeutics; preliminary report. Anesth. & Analg. 29:136 May-June 1950.

10. Mayer, Emil. Toxic effects following use of local anesthetic. J.A.M.A. 82:876 March 15, 1924.

11. Mayer, Emil. Fatalities from local anesthetics. J.A.M.A. 90:1290 April 21, 1928.

12. Ruth, H. S., Haugen, F. P., and Grove, D. D. Anesthesia study commission; findings of 11 years' activity. J.A.M.A. 135:881 Dec. 6, 1947.

13. Dealy, F. N. Anesthetic deaths; 5-year report. Am. J. Surg. 60:63 April 1943.

14. Lefkowitz, L. L. Deaths following use of procaine. Unpublished.

15. Criep, L. H., and Ribeiro, C. C. Allergy to procaine hydrochloride with three fatalities. J.A.M.A. 151:1185 April 4, 1953.

which a local anesthetic was used, a member of the American Society of Anesthesiologists wrote:[16]

> There is a deep rooted impression among doctors that any form of local anesthesia is automatically safer than general anesthesia, and that limited local anesthesia is so innocuous that it may be used on poor risk patients without special precautions. Nothing could be further from the truth. All locally-acting anesthetic drugs have the same inherent dangers of circulatory collapse, if the blood concentration is high, even for a short time.

British anesthetists are even more cautious regarding local anesthesia. Elam[17] quoted Hewer (in *Recent Advances*) who quoted Bortons as finding that in 50,000 unselected and consecutive operations, performed under every variety of local and general anesthesia, the immediate death rate under local anesthesia was more than double that under general anesthesia. Hewer is also stated as quoting Razey who concluded from a study of 21,000 case reports that the adoption of local anesthesia does not in itself diminish the operative mortality. Macintosh[18] stated:

> It is commonly thought that the substitution of a local anesthetic for a general reduces the risk to the patient. I doubt this, and in any case I think that the percentage of fatal accidents with local anesthetics is greater than with general.

Although this obviously is not the case in dental anesthesia, local anesthesias should not be considered a panacea free from fatal complications. Nevertheless, the record of the use of local anesthesia in the dental office is one of which dentistry should be proud and one which other groups associated with the healing arts would do well to study and emulate (Table 2).

■ *Nitrous Oxide-Oxygen*

It is true that the entire group of six general anesthetic deaths in dentistry in New York city during the period 1943 through 1952 were associated with the use of nitrous oxide-oxygen. Still, when it is considered that nitrous oxide-oxygen has been the general anesthetic employed most frequently in the dental offices in New York city in this period, the number of nitrous oxide-oxygen deaths does not appear outstanding. Although Tables 4 and 5 do not reveal the total number of each anesthetic used, they do reveal that nondental anesthetic deaths have occurred with each agent. Anesthetic deaths for a variety of relatively minor procedures were found to be associated with a variety of anesthetics: repair of torn knee ligaments, nitrous oxide-oxygen; fenestration of the ear, intravenous thiopental sodium; skin graft, procaine (local); application of a body cast for a nonexistent fracture of the spine, ether, and so forth. Thus, although there were six nitrous oxide-oxygen deaths in dentistry in these years, it would be remiss to condemn the use of nitrous oxide-oxygen in the dental office.

Any anesthetic used in the dental office, just as any anesthetic used in the medical office or the hospital, has its inherent dangers. The use of nitrous oxide-oxygen may involve a brief hypoxic period, but so may all other anesthetics.

16. Am. Soc. Anesthesiologists New Letter 17:35 Aug. 1953.
17. Elam, J. E. Need for accurate understanding of anaesthetic risks. Brit. J. Anaesth. 19:32 Jan. 1944.
18. Macintosh, R. R. Deaths under anaesthetics. Brit. J. Anaesth. 21:107 Jan. 1949.

Table 4

Anesthetics in fatalities during tonsillectomy and adenoidectomy

	1943	1944	1945	1946	1947	1948	1949	1950	1951	1952	10 yr. total
Nitrous oxide-ether	2				1		2				5
Ether		5	3	3	6	5	4	1	3	1	31
Cyclopropane		1									1
Nitrous oxide-oxygen		1								1	2
Ethyl chloride ether		1							1		2
Vinyl ether (Vinethene)-ether						2					2
Thiopental sodium (Pentothal Sodium)-ether						1					1
Local—procaine			2				1	1		1	5
Local—dibucaine hydrochloride (Nupercaine Hydrochloride)			1								1
Anesthetic unknown			1								1
Total	2	8	7	3	7	8	7	2	4	3	51

Table 5

Anesthetics in fatalities during ophthalmological procedures

Surgical procedure	Anesthetic				Total deaths
	Ether	Intravenous thiopental sodium	Tribromoethanol (Avertin)-ether	Unknown	
Strabismus repair	4		1		5
Cataract repair				1	1
Glaucoma procedure		2			2
Corneal transplant		1			1
Laceration repair	1				1
Evisceration of eyeball				1	1
Eye examination	1				1
Correction of squint	1				1
Other procedures	2				2
Total	9	3	1	2	15

Shaw and co-workers[19] found that anoxia [hypoxia] accompanied cone drop ether anesthesia. McClure and others[20] in a classic study found that narcotics, particularly morphine and barbiturate derivatives, even in moderate doses tend to produce anoxia [hypoxia] of the histotoxic type. These authors found that:

> . . . with this study and comparison of the various commonly used narcotics and anesthetics, it becomes apparent that anoxia [hypoxia] of some degree, and of one or more types usually occurs as a result of their administration. Ordinarily this anoxia [hypoxia] is not of sufficient degree to endanger the patient's life or tissues. . . .

Van Liere[21] stated, "The following produce histotoxic type of anoxia: barbiturates, bromides, urethane, chloral, ether, chloroform, urethene, cyclopropane and to a lesser extent carbon monoxide." The addition of inhalation agents to potentiate nitrous oxide-oxygen anesthesia has increased the range of satisfactory and safe dental office anesthesia. For many years vinyl ether (Vinethene) was the prime adjunct. Recently trichloroethylene has proved to be even more useful as a synergist to nitrous oxide-oxygen anesthesia,[22-24] and hypoxia never need accompany such anesthesia.

It may be said that a listing only of the fatalities involved in the use of nitrous oxide-oxygen anesthesia does not give complete information on the safety factor, since nonfatal cerebral damage has also been reported.[2] Courville's classic monograph[25] often has been quoted to show the nonfatal as well as fatal sequelae of nitrous oxide-oxygen anesthesia-induced cerebral anoxia (hypoxia). It should be pointed out, therefore, that cerebral damage can occur regardless of the cause of hypoxia, if the hypoxic state is of sufficient magnitude and duration. Hoff and co-workers[26] pointed out that the nerve cell damage is essentially the same regardless of the cause or type of anoxia.

Anesthetic-produced hypoxia that results in cerebral damage almost invariably is due to misuse and abuse of the anesthetic or anesthetics. Schreiber,[27] reporting on nine instances of severe cerebral damage and death after the administration of various anesthetics (in five instances, spinal anesthetics), showed that the improper administration of any anesthetic may cause anoxia. Diligent search of the literature has revealed that such cerebral complications after the administration of an anesthetic in a dental office have been rare. Further, there may have been many other complex factors interacting to cause the psychotic or abnormal emotional state that is reported to have followed occasionally nitrous oxide-oxygen anesthesia. Batten and Courville[28] stated as follows:

19. Shaw, J. L., Steele, B. F., and Lamb, C. A. Effect of anesthesia on blood oxygen; study of effect of ether anesthesia on oxygen in arterial and in venous blood. Arch. Surg. 35:1 July 1937.

20. McClure, R. D., and others. Anoxia; source of possible complications in surgical anesthesia. Ann. Surg. 110:835 Nov. 1939; correction 111:160 Jan. 1940.

21. Van Liere, E. J. Anoxia, its effect on the body. Chicago, Univ. Chicago Press. 1942, p. 168.

22. Seldin, H. M., Downs, J. L., and Fierstein, M. Trichloroethylene; safe analgesic for dentistry. New York J. Den. 24:315 Aug.-Sept. 1954.

23. Clement, F. W., and Seldin, H. M. Use of trichloroethylene and thiamylal sodium as adjuncts to other anesthetics in oral surgery. J. Oral Surg. 11:220 July 1953.

24. Seldin, H. M. General anesthetics for office oral surgery. Consultant article. New York D. J. 19:3 Jan. 1953.

25. Courville, C. B. Untoward effects of nitrous oxide anesthesia with particular reference to residual neurologic and psychiatric manifestations. Mountain View, Calif., Pacific Press Publishing Association, 1939.

26. Hoff, E. C., Grenell, R. G., and Fulton, J. F. Histopathology of central nervous system after exposure to high altitudes, hypoglycemia and other conditions associated with central anoxia. Medicine 24:161 May 1945.

27. Schreiber, F. Cerebral anoxia and anesthesia. J. Michigan M. Soc. 38:1950 Dec. 1939.

28. Batten, C. T., and Courville, C. B. Mental disturbances following nitrous oxide anesthesia. Anesthesiology 1:261 Nov. 1940.

No case of post-surgical psychosis can be correctly evaluated until hereditary and environmental factors, habits, and pre-existing disease states as well as the lesion at hand, have been considered as possible etiological factors.

■ *Intravenous Barbiturates*

The use of intravenous anesthetics alone and, more recently, of the combinations of an intravenous barbiturate with nitrous oxide-oxygen has made tremendous gains in anesthesia in the dental office. This is particularly so in the office of the oral surgeon. Many dentists in general practice, however, have adopted intravenous barbiturate anesthesia for use in their offices.

Early reports on its effectiveness and safety by the pioneer workers in intravenous anesthesia in dentistry (men such as Lundy; Pool; Saunders and Narreau; Drummond-Jackson; Thompson; Wyckoff; Hubbell and Adams; Bullard; Thomas, to mention just a few) have been amply confirmed in later studies by Lundy; Olson, Krogh; Thompson and Sleeper; Barton and co-workers; Bullard and Brockett; Millhon; Drummond-Jackson; Everson; Monheim; Ewing; Seldin and so forth.

The research committee of the American Society of Oral Surgeons made a study of anesthetics in 1950 and concluded their report with the following statement:

We sincerely feel that Sodium Pentothal is the safest, the smoothest and most gratifying anesthetic to the patient that we have observed for use by oral surgeons.

Despite a truly enviable safety record, the office administration of intravenous barbiturates for dental procedures is still criticized by some medical anesthetists and dentists. Acknowledging that office administration of thiopental sodium for dental extraction is common, Leffingwell,[29] a medical anesthesiologist, wrote as recently as 1952:

This is a hazardous procedure. . . . The average dose for uncomplicated extraction of one or two teeth will be less than 0.5 gm. If a more extensive procedure is contemplated, it is no longer a legitimate office procedure.

In dentistry, hundreds of thousands of consecutive administrations of intravenous anesthetics without fatality have been reported. Berry[30] reported on over 100,000 administrations of thiopental sodium (Pentothal Sodium) nitrous oxide-oxygen without fatality at the Ewing Clinic. Hubbell[31] has also reported similar absence of fatality in a series of over 100,000 administrations of intravenous barbiturates in the dental office. Krogh, Thompson, Monheim, Levey, Seldin and over a hundred other oral surgeons and anesthesiologists have reported excellent safety records in thousands of administrations of such dental office anesthesia. In the present study there were no deaths attributable to intravenous barbiturate anesthesia in the dental offices of the city of New York. Deaths may occur, however, since the dangers of respiratory depression and laryngospasm are always present. In competent, trained hands, however, this kind of anesthesia is no more dangerous than any other. The anesthetist who can skillfully evaluate his patient, who can prevent laryngospasm and who

29. Leffingwell, F. E. Office practice of anesthesia. J.A.M.A. 148:1181 April 5, 1952.

30. Berry, D. Address delivered before the American Society of Oral Surgeons, Nov. 1954. Unpublished.

31. Hubbell, A. Personal communication.

can manage a spasm should it occur will rarely, if ever, experience a fatality. Intravenous anesthetics, as well as any local, spinal or general anesthetics, are dangerous in untrained or insufficiently trained hands. Rather than condemn the agent, one must emphasize the importance of the skill and training of the anesthetist.

■ *Improvement in Record*

The safety record of dental office anesthesia has improved with time. From Table 1 it can be seen that in the last five years of the study (1948 through 1952) there was only one dental local anesthetic fatality and no dental anesthetic fatality accompanying the use of general anesthetics in New York city dental offices. In the last three years of the study period, no fatalities were reported. Although part of the credit for this record should be attributed to advances in the pharmacology and technics of anesthesia, the improvement is due mainly to the increase in training in anesthesia attained by dentists. This increase has been one of qualitative as well as quantitative preparation, and follows the increasing acceptance by the dental profession of the over-all responsibility of the dentist for the patient who is to have anesthesia in the office.

In 1947, one of us (H.M.S.) published the results of a survey on anesthetics based on replies to questionnaires sent to 207 oral surgeons.[32] Of these oral surgeons, 196 used both general and local anesthetics in their offices. The survey showed that in the five year period ending in 1947, these men had administered or supervised 2,429,148 office anesthesias, during which time there had been 15 fatalities. This represented a mean mortality percentage of 0.0006. It was not surprising, therefore, to learn, as a result of the present study, that anesthesia in the dental office continues to be a widespread, routine, safe procedure.

■ *Summary*

A study of records of deaths in the city of New York for a ten year period was made in order to determine the mortality rate in patients undergoing anesthesia in dental offices. The deaths resulting from administrations of anesthesia for dental procedures were compared with those resulting from administrations of anesthesia for otorhinolaryngological and ophthalmological procedures. The following results were noted:

1. A low percentage (0.43) of dental anesthetic deaths occurred in the ten year period.
2. The percentage of deaths resulting from the use of anesthetics in the dental office was less than that of deaths from the use of anesthetics for otorhinolaryngological and ophthalmological procedures.
3. There were fewer deaths associated with the use of local anesthetics than with the use of general anesthetics.
4. The safety record of dental anesthetics seemed to have improved in the last five years of the period studied.—57 *West Fifty-Seventh Street.*

32. Seldin, H. M. Use of nitrous oxide-oxygen anesthesia in dental surgery. Anesth. & Analg. 26:248 Nov.-Dec. 1947.

Effects of vasoconstrictors used in local anesthetics in patients with diseases of the heart

■ *Irving Salman,* D.D.S., and Sidney P. Schwartz,† M.D., New York*

The purpose of this study was to determine the effect of vasoconstrictors used with local anesthetics in oral surgery on the blood pressure and systemic manifestations of patients with cardiovascular diseases.

A review of the more recent literature on the subject still reveals considerable disparity of views regarding the changes which may result from the use of such vasoconstrictors. For example, Lundy[1] states:

> It would be good judgment to ask every patient more than 45 years of age whether or not he has high blood pressure, kidney disturbance or anything like heart attacks, before Adrenalin-like substances are administered. It is known that these drugs may precipitate a heart attack.

Hickey[2] says that:

> Cardiac complications, such as precordial pain or coronary thrombosis, when they occur, are caused by the vasoconstrictors in the solution and are apt to be serious.

Carr[3] makes the statement that:

> The reduction or elimination of vasoconstrictor agents is desirable. These agents are dangerous, particularly for patients with anginal pain or hypertension.

Hansen[4] points out that:

> Epinephrine should be avoided on hypertension cases.

Harms[5] states:

> The local anesthetic solution used in such a case [patient with cardiovascular disease] should not contain any epinephrine for two reasons: (1) that sympathetic stimulation is induced, which results in tachycardia and (2) vasoconstriction occurs with a resulting elevation of blood pressure which might induce a coronary thrombosis.

Bloom[6] says:

> Aortic regurgitation, mitral insufficiency, exophthalmic goiter, arteriosclerosis and hypertension, indicate the use of Novocaine without epinephrine content.

Further confusion is added by the following remarks: Miller[7] claims that:

> Generally speaking, it is our impression that disturbing clinical symptoms were mild or absent, when weaker concentrations of epinephrine or Cobefrin were injected.

Borg[8] states:

*Director and attending oral surgeon, Beth Israel Hospital; visiting oral surgeon, Montefiore Hospital; assistant professor of oral surgery, New York University College of Dentistry.

†Cardiographer and attending physician, Montefiore Hospital; assistant clinical professor of medicine, Columbia University.

1. Lundy, C. J. What the patient should know about angina pectoris, coronary thrombosis and arteriosclerosis. D. Digest 45:104 March 1939.

2. Hickey, M. J. Local anesthesia in oral surgery. J.A.D.A. 33:1532 Dec. 1946.

3. Carr, M. W. Heart disease: prophylactic and therapeutic management of the patient in dental practice. J.A.D.A. 36:253 March 1948.

4. Hansen, O. S. Common sense about heart disease. D. Digest 38:220 June 1932.

5. Harms, B. H. Anesthetics and their side actions in oral conditions. J.A.D.A. 22:943 June 1935.

6. Bloom, D. D. A consideration of procaine anesthesia for dental purposes. D. Cosmos 76:1094 Oct. 1934.

7. Miller, H. C. Clinical reactions to various anesthetic solutions. J.A.D.A. & D. Cosmos 24:515 April 1937.

8. Borg, F. H. Effect of procaine-epinephrine solutions on the pulse rate and blood pressure. J.A.D.A. 21:868 May 1934.

Small dosage of procaine epinephrine, as employed in local anesthetic solutions, has no consistent relation to the variations observed in pulse rate or blood pressure.

Blumgart[9] says:

After injection of 0.5 to 1.0 cc. of 1:1,000 solution (epinephrine) subcutaneously, in ten normal subjects, under strict basal conditions, the systolic blood pressure rose in all instances from 10 to 70 mm. of mercury, average being 38. The diastolic pressure remained unchanged in three subjects but fell from 5 to 35 mm. of mercury in the remaining, an average of 14.

Starr and co-workers[10] injected epinephrine in an average dose of 0.7 cc. of 1:1,000 solution and wrote that:

The increase in systolic and decrease in diastolic pressures indicate that the epinephrine is a powerful cardiac stimulant in man and that after subcutaneous injection, the diastolic pressure usually falls, due to vasodilation in certain vessels predominating over the vasoconstriction which undoubtedly occurs in other areas.

Tainter and Winter[11] found

. . . that the systolic and diastolic blood pressures were no greater in hypertensive groups of patients than in the normal individuals.

Most dental and medical schools still teach that epinephrine-like substances should not be used in combination with local anesthetics in patients with heart disease. Most physicians still warn dentists against the use of epinephrine and even advise patients with cardiovascular diseases not to permit their dentist to use epinephrine with local anesthetics.

■ *Method of Study*

Both ambulatory and nonambulatory patients from the Montefiore and Beth Israel Hospitals were studied. The injection of local anesthetic solutions containing a vasoconstrictor, as well as the blood pressure readings, was carried out by the internes of the two hospitals. Blood pressure readings were taken prior to, immediately after and at intervals of two and five minutes respectively after the injections, and more often when found necessary in order to be sure that the peak of the action of the drugs was not missed. Records were kept of any systemic manifestations such as tremors, sweating, pallor or nausea or any other clinical signs.

The following drugs were used as combined anesthetics and vasoconstrictors:

Butethamine hydrochloride 1.5 per cent and 1:100,000 epinephrine.

Procaine 4 per cent and phenylephrine

Procaine 2 per cent and nordefrin hydrochloride 1:10,000

Procaine 2 per cent and epinephrine 1:50,000

Butethamine hydrochloride 1.5 per cent and Neosupranol 1:250

Butethamine hydrochloride 1.5 per cent and Neosupranol 1:500

The patients have been divided into nine groups. Group 1 is composed of 45 nonambulatory patients from the Montefiore Hospital who had a variety of chronic diseases but no involvement of the cardiovascular system. This group was used as a control.

9. Blumgart, H. L. Circulatory response to epinephrine. In Contributions to the medical sciences in honor of Dr. Emanuel Libman by his pupils, friends and colleagues. New York, International Press, 1932.

10. Starr, S., and others. Clinical study of the action of 10 commonly used drugs on cardiac output, work and size; on respiration, on metabolic rate and on the electrocardiogram. J. Clin. Investigation 16:799 Sept. 1937.

11. Tainter, M. L., and Winter, L. Some general considerations in evaluating local anesthetic solutions in patients. Anesthesiology 5:470 Sept. 1944.

Table 1

Average rise of blood pressure

Group no.	Systolic			Diastolic		
	Immediate	2 min.	5 min.	Immediate	2 min.	5 min.
1	7.31	8.24	7.20	7.31	6.94	7.70
2	9.30	8.40	7.52	8.12	7.44	6.30
3	10.36	9.83	8.66	10.44	5.00	3.46
4	11.66	4.74	11.42	11.39	3.92	7.75
5	10.75	8.77	4.66	6.69	4.7	3.00
6a	10.0	14.0	12.00	10.1	6.66	4.5
6b	10.8	7.0	2.66	9.4	8.50	8.25
7	7.68	7.69	6.73	8.25	6.64	7.26
8	9.0	7.04	6.15	7.46	8.25	6.6
9	8.63	7.42	7.45	7.42	6.54	6.43

Group 2 consists of 181 nonambulatory patients with cardiovascular involvements from the Montefiore Hospital. Group 3 is composed of 33 ambulatory patients with cardiovascular diseases from the Beth Israel Hospital. The patients in this group were from the outpatient department of the hospital and could be considered comparable to patients that might be encountered in an average office practice; that is, patients in whom local anesthetics are used when surgical intervention is required.

Group 4 is comprised of 46 nonambulatory patients from the Montefiore Hospital with hypertensive cardiovascular disease. Group 5 includes 20 ambulatory patients from the Beth Israel Hospital also with hypertensive cardiovascular disease. Among these groups the youngest patient was 6 years of age and the eldest was 74.

Group 6a and 6b are made up of 12 patients from the control group. The patients in Group 6a were given an injection of normal saline solution prior to the injection of the local anesthetic. Subsequently, the same patients (Group 6b) were given a local anesthetic with a vasoconstrictor. Blood pressure readings were taken after the injection of salt solution and after the anesthetic solution.

The 41 cardiovascular disease patients in Group 7 were normotensive, and the 51 cardiovascular disease patients in Group 8 were hypotensive. Group 9 consists of 56 children with either congenital malformations of the heart or chronic rheumatic valvular heart disease.

Blood pressure readings of 120 mm. of mercury systolic and 90 mm. of mercury diastolic were regarded as normal. Systolic blood pressure readings of 150 mm. of mercury and 90 mm. of mercury for diastolic were considered as the low for the hypertensive group. A systolic figure below 110 mm. of mercury was considered as relatively low blood pressure.

■ *Summary*

When the rises of blood pressure only are considered:

1. In general the greatest average rise in systolic and diastolic blood pressure in the cardiac disease groups occurred earlier than in the control group and was somewhat higher (Table 1).

Table 2

Average fall of blood pressure

Group no.	Systolic			Diastolic		
	Immediate	2 min.	5 min.	Immediate	2 min.	5 min.
1	7.25	7.9	7.29	3.70	4.18	3.28
2	5.83	7.42	7.87	6.13	6.99	8.01
3	6.44	10.0	10.4	8.87	7.00	9.0
4	4.71	9.26	10.58	3.56	3.92	8.73
5	5.55	9.77	11.27	4.0	4.75	7.5
6a	10.0	6.66	8.0	6.66	7.75	7.5
6b	8.0	12.25	11.4	9.4	8.4	10.1
7	2.16	8.37	7.8	6.33	6.79	6.77
8	7.77	7.13	6.08	5.41	4.37	6.35
9	4.88	5.61	4.86	7.59	7.55	7.22

Table 3

Average of combined rise and fall and no-change values of blood pressure

Group no.	No. of subjects	Systolic			Diastolic		
		Immediate	2 min.	5 min.	Immediate	2 min.	5 min.
1	45	+2.8	+2.5	+0.2	+2.9	+1.9	+1.2
2	181	+4.9	+3.2	+1.3	+2.2	+1.2	−0.4
3	33	+5.0	+2.3	−2.2	+4.0	0.0	−0.6
4	46	+8.4	−0.2	+0.4	+2.4	+0.9	−1.8
5	20	+4.8	−0.5	−5.8	+3.8	+1.4	+0.6
6a	12	+5.0	+3.0	−3.7	+3.4	−0.9	−2.3
6b	12	+4.3	−1.2	−4.1	0.0	+0.8	−2.3
7	41	+4.8	+3.8	+1.7	+2.2	+0.4	+0.5
8	51	+2.1	+1.6	+1.0	+1.7	+1.9	+1.0
9	56	+4.6	+3.5	+2.6	+0.9	+0.1	−0.1
Total	495						

When the decreases in blood pressure only are considered:

2. The greatest average fall in systolic and diastolic pressure in cardiac disease groups occurred somewhat less frequently immediately after injection than later (Table 2).

When the rises and decreases in blood pressure are considered in combination:

3. In most groups (control and cardiac disease), there was a decrease in average systolic and diastolic blood pressure from that immediately after the injection to five minutes after injection (Table 3).

4. In all groups (with the exception of one group, 6b) there was an average rise of systolic and diastolic blood pressure immediately after injection (Table 3).

5. This average rise in systolic blood pressure in the cardiac disease group was, with one exception (Group 8), 1.5 to 5.6 mm. of mercury greater than the rise in the control group immediately after injection (Table 3).

Table 4

Percentage of individuals with rise, fall and no change in blood pressure

Group No.		Systolic			Diastolic		
		Immediate	2 min.	5 min.	Immediate	2 min.	5 min.
1	R	64	55	43	56	46	29
	F	27	27	40	31	30	31
	N	9	18	17	13	24	40
	No.	45	38	35	45	37	35
2	R	64	63	49	50	47	41
	F	19	27	31	30	33	38
	N	17	10	20	20	20	21
	No.	181	174	166	179	175	165
3	R	58	55	31	49	43	41
	F	27	33	47	24	30	22
	N	15	12	22	27	27	37
	No.	33	33	32	33	33	32
4	R	78	59	43	35	54	36
	F	15	32	43	50	31	50
	N	7	9	14	15	15	14
	No.	46	46	44	46	46	44
5	R	60	45	16	65	50	47
	F	30	45	58	15	20	11
	N	10	10	26	20	30	42
	No.	20	20	19	20	20	19
6a	R	59	33	8	55	25	33
	F	8	25	58	27	33	50
	N	33	42	34	18	42	17
	No.	12	12	12	11	12	12
6b	R	58	42	25	42	50	33
	F	25	33	42	42	42	50
	N	17	25	33	16	8	17
	No.	12	12	12	12	12	12
7	R	68	71	54	49	42	36
	F	22	19	24	29	34	32
	N	10	10	22	22	24	32
	No.	41	41	41	41	41	41
8	R	47	51	39	47	39	39
	F	26	27	24	33	31	28
	N	27	22	37	20	30	33
	No.	51	51	51	51	51	51
	R	63	64	52	43	43	38
	F	16	23	27	30	36	32
	N	21	13	21	27	21	30
	No.	56	56	56	56	56	56

R = rise
F = fall
N = no change
No. = number of individuals

6. This difference between the control and cardiac disease groups in average systolic blood pressure did not obtain at the two minute and five minute intervals (Table 3).

When the percentage of individuals experiencing rise, fall, or no change in blood pressure is considered:

7. In all groups (control and cardiac) there was a greater percentage of individuals who experienced a rise in systolic blood pressure immediately after injection than a fall or no change; the number of those experiencing a rise varying from 47 to 78 per cent (Table 4).

8. This tendency was generally maintained at the two minute interval but was not consistently present at the five minute interval (Table 4).

9. With the exception of two groups (4 and 6b), there was a greater percentage of individuals in all groups who experienced a rise in diastolic blood pressure immediately after injection, the number of those experiencing a rise varying from 35 to 65 per cent (Table 4).

10. This tendency was maintained at the two minute interval but not at the five minute interval (Table 4).

There were no untoward effects observed clinically either in the patients with cardiovascular disease or in the control group after the injection of vasoconstrictors with local anesthetics. Some isolated clinical manifestations such as pallor and trepidation were probably caused either by psychic reaction or possibly by the systemic effect of the drug. Such phenomena are transitory and are observed at times in patients without cardiovascular disease as well as in patients with heart disease.—250 *West Fifty-seventh Street.*

■ COMPETENCE

I would have you look carefully and recognize by eye when you are attending dissections or when you see anyone else who may be better supplied with instruments than yourself. For my judgment is that it is much better that you should learn the manner of cutting by eye and touch than by reading and listening. For reading alone never taught anyone how to sail a ship, to lead an army, nor to compound a medicine, which is done rather by the use of one's own sight and the training of one's own hands. *Jacobus Sylvius, "Introduction to Anatomy."*

Review of antibiotics

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The antibiotics are probably the most important of all drugs that the oral surgeon of today has at his disposal. They represent a group of therapeutic agents which have been developed during the last ten years. Last year the antibiotics accounted for about 20 per cent of the total drug sales in the United States ($328,000,000 at the manufacturers' level.)[1]

The principal antibiotics in therapeutic use today include penicillin, U.S.P.; streptomycin, U.S.P.; bacitracin; neomycin, N.N.R.; polymyxin B, N.N.R.; chlortetracycline (Aureomycin, U.S.P.); oxytetracycline, (Terramycin, N.N.R.); chloramphenicol, U.S.P. (Chloromycetin); erythromycin, N.N.R.; tetracycline (Achromycin, Tetracyn); and tyrothricin, N.N.R. (see table).

The oral surgeon is concerned primarily with those antibiotics that will keep under control organisms normally or abnormally found in the oral cavity. These include mainly gram-positive streptococci and staphylococci; spirochetes and fusiform bacilli may be present in chronic periodontal disease.

■ *Penicillin*

Penicillin is the oldest and still the most widely used antibiotic. In contrast to many other antibiotics, penicillin is primarily bactericidal, but it is also bacteriostatic. The nature of the bactericidal action is not entirely clear, but there is evidence that this action is due to interference with the metabolic processes of a microorganism. Pharmacologically, penicillin is practically inert.

The most prominent advances in penicillin therapy have been the following: (1) the gradual change from intramuscular preparations which are rapidly absorbed and rapidly eliminated, to those which are slowly absorbed and thus maintain an elevated blood level for a prolonged period of time, (2) the preparation of several products for intramuscular use which are rather rapidly absorbed and which produce, for a brief period of time, an extremely high tissue concentration and (3) the development of penicillin particularly adapted for oral medication.

For intramuscular use, procaine penicillin G, which is a stable crystalline salt, is available in several forms:

1. Procaine penicillin G (not fortified) containing 300,000 units per milliliter is the preparation most frequently used when it is desired to maintain, with a single intramuscular injection, a low blood level for two or three days.

2. Procaine penicillin in oil with 2 per cent aluminum monostearate (P.A.M.) comes in a dose of 300,000 units, and is used to maintain an effective blood level for four days.

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1. Parade of new antibiotics. Food & Drug Res. June 1954.

3. When a really high tissue concentration is desired in 30 to 60 minutes, then procaine penicillin G (300,000 units per milliliter) fortified with 100,000 units of crystalline potassium penicillin is the drug of choice.

Other new penicillin preparations for intramuscular use that deserve consideration include diethylaminoethyl ester hydriodide of penicillin G (Neo-Penil) and benzathine penicillin G (Bicillin). Neo-Penil is used to produce relatively high concentrations of penicillin in lung tissue, salivary glands or in the brain. Obviously, this drug should not be given to a patient who has demonstrated sensitivity to iodides or to penicillin.

Benzathine penicillin G also represents a repository penicillin; it is N,N'-dibenzylethylenediamine dipenicillin G. This preparation is rapidly becoming the drug of choice when it is desired to use penicillin for a long-term program of prophylaxis. A modification of this preparation is Bicillin C-R; this contains per milliliter 300,000 units of procaine penicillin and 300,000 units of benzathine penicillin G and produces a relatively high penicillin level for 24 hours, and a low level for one week. An All-Purpose Long Acting Bicillin is now available. This contains 300,000 units procaine penicillin G, 300,000 units potassium penicillin G, and 600,000 units benzathine penicillin G per milliliter. One intramuscular injection of this drug produces a high initial penicillin level and a prophylactically effective level for 10 to 12 days.

Table

Principal antibiotics in use today

Group	Name	Effective agst. organisms which are		Broad-spectrum antibiotic (Rickettsia, large viruses)	Treatment of systemic infection			Treatment of conditions in enteric tract and so forth (orally)	Applied locally
		Gram +	Gram −		Orally	Intra-musc.	Intra-ven.		
1	*Penicillin	X†	(X)‡		X	X			(X)
	Streptomycin and dihydrostreptomycin	X	(X)			X		X	X
	*Bacitracin	X				(X)		X	X
	Neomycin	X	X			(X)		X	X
	Polymyxin B		X			X		X	X
	*Oxytetracycline	X	(X)	X	X		(X)		(X)
2	*Chlortetracycline	X	(X)	X	X		(X)		(X)
	*Tetracycline	X		X	X				
	Chloramphenicol	(X)	X	X	X	(X)	(X)		(X)
	Erythromycin	X	(X)	X	X				X
	Tyrothricin (containing gramicidin and tyrocidine)	X	(X)						X

*Antibiotics of primary interest to the oral surgeon.
†X, primary effect or use.
‡(X), effect or use of secondary importance.

Of particular interest to the oral surgeon is penicillin for oral use.[2,3] After ingestion of this antibiotic, absorption from the duodenum is evident in 10 to 20 minutes. The maximal concentration in the blood is reached in less than one hour, but the peak usually persists for no longer than 30 minutes. To obtain equivalent effects requires approximately 1,000,000 units by mouth for each 300,000 units given intramuscularly.

Two oral preparations of benzathine penicillin G, one liquid and the other in tablet form, are available which, according to Welch,[4] present an improvement over other commercially produced oral preparations. Since the drug is without taste and since its solubility in water is adequate (0.02 per cent), it has been possible to prepare an effective liquid oral suspension (300,000 units per 5 ml.). At present this is being used a great deal by pediatricians. The second preparation is a 200,000 unit tablet. This tablet if taken every 10 to 12 hours will induce a continuous demonstrable blood concentration in most patients. Stollerman[5] (cited by Welch), in a preliminary report, called attention to the use of oral benzathine penicillin G (Bicillin) for prophylactic use in patients with rheumatic fever. Keefer[6] stated that he finds oral administration of penicillin extremely effective for the treatment of mild and moderately severe systemic infections due to gram-positive microorganisms; he administers 200,000 to 400,000 units three times a day.

Another mode of administration to be mentioned is the inhalation of penicillin dust or of aerosol solutions for the purpose of reducing the gram-positive bacterial flora in the throat, sputum and nose. Only about one third of the nebulized penicillin is absorbed. There appears to be no advantage of this type of medication over oral or intramuscular therapy. Also, the material is likely to cause local irritation.

In regard to the use of a penicillin-containing dentifrice, it is acknowledged that penicillin, in this form, will reduce the bacterial flora in the mouth, and it has been reported that it may aid in lowering the incidence of dental caries. The danger of producing resistant strains and severe penicillin sensitivities if utilized in this fashion, however, cannot be overlooked.[7] For this reason the Council on Dental Therapeutics of the American Dental Association[8] has seen fit to recommend that penicillin dentifrices be made available only on a prescription basis.

The clinical indications for penicillin and other antibiotics include their use for prophylaxis from and resolution of bacteremia after tooth extraction. This is particularly important in patients with organic valvular heart disease, rheumatic fever, arteriosclerosis, renal diseases and diabetes. Prophylactic therapy is also important in the prevention of streptococcal infections, and in reducing the recurrence of rheumatic fever.

2. Fairbrother, R. W., and Daber, K. S. Oral penicillin. Lancet 1:858 April 24, 1954.

3. McCarthy, F. P., and McCarthy, P. L. Diseases of the mouth; statistical review of 4,728 patients. New England J. Med. 250:493 March 25, 1954.

4. Welch, H. Newest addition to the repository penicillins; dibenzylethylenediamine dipenicillin. Antibiotics & Chemother. 3:347 April 1953.

5. Stollerman, G. H., and Rusoff, J. H. Prophylaxis against Group A streptococcal infections in rheumatic fever patients. J.A.M.A. 150:1571 Dec. 20, 1952.

6. Keefer, C. S. Evaluation of antibiotic therapy. Diplomate 23:216 Oct. 1951.

7. Perrin, L. H. Clinical use of antibiotics in dental infections. (Abst.) Upjohn Co. Sheet no. 13,548 June 1951.

8. Council reports on current status of penicillin. Council on Dental Therapeutics, American Dental Association. (Abst.) Upjohn Co. Sheet no. 17,391 Oct. 1952.

In a paper published recently, Pressman and Bender[9] recommended the cooperation of the dentist and the physician in pointing out to a patient with a history of rheumatic diseases and so forth, the danger associated with a simple surgical procedure such as tooth extraction or similar dental manipulation. They recommended the following regimen:

1. One hour before tooth extraction: 300,000 units of aqueous procaine penicillin and 100,000 units of crystalline penicillin intramuscularly, in combination with 1.0 Gm. of streptomycin intramuscularly.

2. Thirty minutes before extraction: a troche, containing 200,000 units of penicillin, 50 units of bacitracin and 0.12 Gm. of sulfadiazine.

3. Twelve to 24 hours after extraction: but only if considered necessary, an additional injection of penicillin and streptomycin.

Pressman and Bender expressed the belief that antibiotic medication earlier than one hour preoperatively is unnecessary. Nathanson[10] used one of the newer penicillin preparations. He recommends Bicillin-SR for third molar surgery, cysts and alveoplastic procedures in the absence of acute infections.

In another investigation Nathanson and his co-workers,[11] in agreement with observations reported by Mallett and also Williams,[11] found that injection of a dose equal to 600,000 units of benzathine penicillin G (Bicillin) is sufficient for prophylaxis in all types of dental surgery on patients with relatively healthy mouths. They recommended for treatment of acute dental infections, or for surgery in the presence of pre-existing infection, the injection of 600,000 units of benzathine penicillin G which was supplemented by the administration of 300,000 units of procaine penicillin and 100,000 units of aqueous crystalline penicillin.

When the oral surgeon finds it necessary to treat a patient who is being treated by a physician for bacterial endocarditis, then more intensive therapy based on quantitative sensitivity studies is indicated. Cossio and Berreta[12] reported clinical and bacteriological cures in 38 of 63 such patients. Most of these were treated by the intramuscular route with penicillin, 300,000 units every three hours, and with streptomycin, in doses of 0.5 Gm. every 12 hours. Both drugs were given for a period which ranged from four to five weeks. A more favorable report for this kind of combined therapy was published by Robbins and Tompsett.[13]

The question of using penicillin with another antibiotic deserves special consideration. If it is remembered that penicillin and other antibiotics, as well as the sulfonamides, have selective and overlapping antibacterial spectrums, and that each of the antibiotics when given with another antibiotic may demonstrate either synergism, a simple additive effect, or antagonism, then laboratory and clinical

9. Pressman, R. S., and Bender, I. B. Dental extractions and their relationship to subacute bacterial endocarditis. J. Albert Einstein Med. Center 1:94 Feb. 1953.

10. Nathanson, I. G. Review of the antibiotics—their applicability to the general dental practitioner. Mimeographed.

11. Nathanson, I. G., Morin, G. E., and Mallett, S. P. Dibenzylethylenediamine dipenicillin G (Bicillin) in dental use; clinical observations on 150 patients. Antibiotics & Chemother. 3:368 April 1953.

12. Cossio, P., and Berreta, J. A. Antibiotics in heart diseases. (Abst.) J.A.M.A. 154:721 Feb. 20, 1954.

13. Robbins, W. C., and Tompsett, R. Treatment of enterococcal endocarditis and bacteremia: results of combined therapy with penicillin and streptomycin. (Abst.) Upjohn Co. Sheet no. 12,849 March 1951.

experience will determine which antibiotics should be employed simultaneously. In general, combined therapy should be considered only for the following: (1) prophylaxis before an operation, (2) mixed infections and (3) the treatment of infections of obscure etiology.

Jawetz and others[14-17] found in laboratory studies that penicillin, streptomycin, bacitracin, neomycin and polymyxin B belong to one group of antibiotics, all of which are strongly bactericidal (Group 1), and that oxytetracycline, chlortetracycline, tetracycline and chloramphenicol belong to another group which are primarily bacteriostatic (Group 2). Jawetz and his co-workers expressed the belief that the bacteriostatic drugs through their inhibition of growth of an organism somehow prevent a bactericidal agent from exerting its full effect. Hence they recommended that a drug of Group 1 not be administered with a drug of Group 2.

According to Groel, this theory is supported by considerable *in vivo* experimentation, but it has been neither proved nor disproved in clinical practice. No final statement, therefore, can be made at this time. It is primarily on these theoretical grounds, however, that most oral surgeons do not use antibiotics of these two groups simultaneously. They do not hesitate, however, to use two drugs of one group plus a sulfonamide. One such example is the combination of penicillin with streptomycin and sulfadiazine. Penicillin and streptomycin may even be given together in the same syringe.[18] Gray[19] for one, is willing to depart from the above conception. He stated the following:

In patients with mixed infections and with infections due to *Micrococcus pyogenes* (*aureus*) (*Staphylococcus aureus*) resistant to penicillin, a combination of penicillin and chloromycetin might be justifiable.

Price and others[20] in *in vivo* tests with animals found that streptomycin had a synergistic action when given with chlortetracycline, sulfadiazine, sulfamerazine and sulfathiazole.

Certain side effects or signs and symptoms of toxicity have been observed after penicillin medication. The most serious are anaphylactoid reactions. Last year, officials of the Federal Food and Drug Administration carried out a survey covering 95 hospitals. They discovered 63 anaphylactoid reactions not previously reported which were due to antibiotics. If 25 reactions which the Smith, Kline and French Company[21] reported to the Federal Food and Drug Administration were added, then the record, incomplete as it is, emphasizes that the occurrence of an anaphylactoid reaction is more frequent than is generally recognized. This reaction is characterized by rapid onset of cyanosis, coughing, tonic spasms, gasping, a weak and thready pulse and a severe drop of blood pressure.

14. Jawetz, E., and Gunnison, J. B. Studies on antibiotic synergism and antagonism: a scheme of combined antibiotic action. Antibiotics & Chemother. 2:243 May 1952.

15. Jawetz, E., and Gunnison, J. B. Antibiotic synergism and antagonism. New England J. Med. 245:966 March 1951.

16. Jawetz, E., and Gunnison, J. B. Experimental basis of combined antibiotic action. Report to Council on Pharmacy and Chemistry. J.A.M.A. 150:693 Oct. 1952.

17. Gunnison, J. B., Jawetz, E., and Coleman, V. R. Effect of combinations of antibiotics on enterococci in vitro. J. Lab. & Clin. Med. 36:900 Dec. 1950.

18. Queries and minor notes. Combination of antibiotics. J.A.M.A. 139:272 Jan. 22, 1949.

19. Gray, J. P. Personal communication, 1954.

20. Price, C., and others. Studies of combined action of antibiotics and sulfonamides. (Abst.) Upjohn Co. Sheet no. 7,213 March 1949.

21. Status of Neo-Penil in regard to toxicity. Medical Department, Smith, Kline and French Laboratories, Philadelphia, 1954.

Anaphylactoid reactions have been noted most frequently after intramuscular injections of penicillin. One should not forget that oral and topical administration of this antibiotic also are capable of producing fatalities, and that anaphylactoid reactions may suddenly develop in a patient who was previously treated with penicillin without showing signs of hypersensitivity. If one considers the tremendous tonnage of penicillin that has been used, then, perhaps, the incidence of anaphylaxis is still relatively infrequent. Significant, however, is the fact that many of these severe reactions could have been avoided, had adequate precautions been observed.[22, 23]

A second group of reactions, which are noted in 2 to 5 per cent of patients, and which are generally not dangerous but often are extremely annoying to a patient, include localized or generalized urticaria, arthralgia, pruritus, edema, sore throat, fever, headache, nausea, proteinuria and leukocytosis. These signs may appear as late, or last as long, as two weeks after the administration of penicillin.[24]

In a study involving 1,753 intramuscular injections of benzathine penicillin G (Bicillin) in 135 children and eight adults, it was concluded that local reactions are somewhat more severe after the injections of benzathine penicillin G than after the injections of penicillin G or procaine penicillin.[5] On the whole, men are more susceptible than women, whereas children of both sexes are affected the least. According to Beckman[25] localized reactions due to penicillin administered orally may include discoloration of the tongue, stomatitis and glossitis. With the exception of one serious case, the oral administration of benzathine penicillin G (Bicillin) has not resulted in toxic reactions except for changes in the consistency of stools. Caution is in order, however, since benzathine penicillin G has not yet been used extensively. According to Babcock,[26] reactions to penicillin are increasing rapidly, not only the simple urticarial type but also those that are serious and fatal.

Penicillin aerosols and dusts are known to have produced in roughly every tenth patient a black, hairy tongue and local reactions within the mouth. Application of ointments of penicillin to the skin may induce erythematous and vesicular reactions, but what is more dangerous, they may sensitize the patient systemically.

Briefly, the precautions to be observed with penicillin therapy are as follows:

1. Penicillin by any mode of administration is to be avoided, or given with the greatest caution, to a patient with a history of bronchial asthma, hay fever, urticaria, angioneurotic edema or to one having demonstrated a previous sensitivity to penicillin.

2. If a penicillin-sensitive patient must receive penicillin, allergic reactions may be greatly diminished by prior injection of an antihistamine. Chlorprophenpyridamine maleate (Chlor-Trimeton

22. Altounyan, E. H. R. Fatality following penicillin injection. Brit. M. J. 2:1375 Dec. 19, 1953.

23. Higgins, G. A., and Rothchild, T. P. E. Fatal anaphylactic shock from procaine penicillin. New England J. Med. 247:644 Oct. 23, 1952.

24. Farrell, John J. Personal communication.

25. Beckman, H. Pharmacology in clinical practice. Philadelphia, W. B. Saunders Co., 1953.

26. Babcock, G., Jr. Personal communication.

Maleate), 10 mg. just before each intramuscular injection, has given good results.[27]

The use of an intradermal skin test will single out effectively those individuals who are seriously allergic to penicillin. The test as developed and used by Dr. M. Jay Flipse[28] is as follows:

An aqueous solution of crystalline penicillin containing 25,000 to 50,000 units per cubic centimeter is prepared (it retains its antigenicity potency for a long time when kept in the icebox—even though it may not retain its bactericidal potency). Inject 0.05 to 0.1 cc. intradermally into the skin of the flexor surface of the forearm, producing a small bleb. Examine in 15 to 30 minutes. An increase in the size of the bleb without local redness or pseudopod reaction is normal. The development of pseudopods or an irregular outline of the bleb either with or without an area of pallor or erythema indicates sensitivity to the drug. If slight, penicillin will be tolerated for a few doses without serious reactions. If severe, do not give penicillin.

3. Penicillin treatment should be discontinued if signs or symptoms of toxicity appear, such as anaphylactoid-type effects, exfoliative dermatitis, or pulmonary edema.

4. When the drug is given intramuscularly, accidental intravenous injection must be avoided.

5. For oral use, and whenever possible, penicillin tablets should be prescribed in number equal to the number of tablets in a single container.[29]

6. The use of penicillin troches or dentifrices should be avoided.

■ *Streptomycin*

Streptomycin has bactericidal properties similar to those of penicillin, but its use today is rather well restricted to the treatment of tuberculosis, infections of the urinary tract and enterococcic endocarditis.[30] Largely because of its toxicity and the rapid development of bacterial resistance to it, streptomycin is slowly being replaced by chlortetracycline, oxytetracycline and chloramphenicol. Streptomycin has been given together with penicillin and followed by sulfadiazine for the treatment of mixed bacterial infections.[18]

Side effects most frequently noted in patients are vestibular damage, vertigo, visual difficulties, renal complications and sensitization. Damage to the vestibular apparatus may be sufficiently serious to incapacitate an individual, preventing him from driving a car, walking in the dark, or from crossing a congested street. Nausea, anorexia, vomiting and vertigo frequently appear during the third or fourth week of treatment.[31] Nerve damage, dizziness, vertigo or ataxia have been noted in about half of the patients receiving more than 1.0 Gm. per day. Recovery is slow, and not always complete.

Administration of a therapeutic dose of streptomycin to a sensitized person may prove fatal. Desensitization, therefore, is in order if this drug must be given to such a patient. Signs and symptoms of hypersensitivity become manifested as drug fever, urticaria, dermatitis, aplastic anemia and asthma.

The injection of streptomycin should

27. Beck, C. A. Subacute bacterial endocarditis in penicillin-sensitive patient. J.A.M.A. 153:1170 Nov. 28, 1953.

28. Flipse, M. Jay. Personal communication.

29. Foreign letters. Faulty penicillin tablets. J.A.M.A. 154:607 Feb. 13, 1954.

30. Kirby, W. M. M. Recent trends in antibiotic therapy. J.A.M.A. 144:233 Sept. 16, 1950.

31. Streptomycin in the treatment of tuberculosis; official memorandum. Lancet 1:273 Feb. 12, 1949.

be made with a rigorously aseptic technic so as to avoid abscesses at the site of injection.

Those who handle or administer streptomycin should wear rubber gloves when doing so, in order to avoid the development of sensitivity.

Stable solutions prepared by a pharmaceutical house that contain 0.25 per cent phenol are preferable to solutions prepared by the one administering the drug.[32]

The closely related antibiotic dihydrostreptomycin was introduced as a substitute for streptomycin. Original claims for a lower degree of toxicity did not prove correct. According to Beckman:[25]

> . . . we now know that the new drug is much more toxic to the auditory nerve than the older one. Not only does it cause a disturbance of hearing in a high proportion of patients taking it, but some become permanently "stone" deaf. . . . This drug should not be used unless circumstances seem to make it absolutely necessary.

■ *Bacitracin*

The antibacterial spectrums of bacitracin and penicillin are similar; therefore, the use of bacitracin is permissible when penicillin sensitivity exists.

The drug has been used most extensively in an ointment for the treatment of surface infections. It has also been used for local injection into lesions such as superficial and deep abscesses, carbuncles and sties. Troches (Bacipharyn Troches) which contain 1,000 units of bacitracin and 5 mg. ethyl aminobenzoate are available for the treatment of infections of the mouth. In a recently published report, reference is made to a bacitracin-neomycin combination which was used for the treatment of pyogenic dermatoses.[33] In 53 patients treatment was successful; in five it was not. Solutions for local application (500 units per milliliter) may also be instilled into the eye for treatment of a sty or similar disorders.

Local sensitization and cutaneous moniliasis have not been reported. Most of the antibiotics, other than penicillin, are derived from various species of *Streptomyces* isolated from the soil all over the world. There is less tendency to allergy to these antibiotics, therefore, than to penicillin.[28]

The drug is only slightly absorbed when given by mouth. Most, Miller and Grossman[34] used it for the treatment of amebic colitis and found it very promising. They gave 80,000 units daily for ten days.

After an intramuscular injection of 10,000 units, therapeutically effective blood levels persist for seven to eight hours. Friedberg and Bader[35] reported on a patient suffering from staphylococcic endocarditis who was treated successfully with 660,000 units of bacitracin given intramuscularly in divided doses over a period of 15 days. This patient had not responded to penicillin, chlortetracycline and chloramphenicol. Longacre and Waters[36] reported on 50 patients who

32. Medical memoranda. Contamination of streptomycin solutions with resistant bacteria. Brit. M. J. 2:87 July 10, 1954.

33. Lubowe, I. I. Treatment of pyogenic dermatoses with a bacitracin-neomycin ointment. Am. Pract. & Digest Treatment 4:625 Sept. 1953.

34. Most, H., Miller, J. W., and Grossman, E. J. Treatment of amebiasis with bacitracin and other antibiotics. Am. J. Trop. Med. 30:491 July 1950.

35. Friedberg, C. K., and Bader, M. E. Acute staphylococcic endocarditis cured with the aid of bacitracin. J.A.M.A. 147:46 Sept. 1, 1951.

36. Longacre, A. B., and Waters, R. M. Parenteral bacitracin in surgical infections. Am. J. Surg. 81:599 June 1951.

were treated for various kinds of systemic infections. Two of the patients received eight injections of 5,000 units each, others were given 23,000 to 50,000 units per dose with total doses up to 1,000,000 units. Of these, 68 per cent responded favorably. Side effects, primarily albuminuria and pain at the site of injection, occurred in one third of the patients. These effects had no relation to the size of the dose, duration of therapy, type of infection or lot of the drug. They disappeared promptly when therapy was discontinued.

■ *Neomycin*

Neomycin is one of the newer antibiotic agents which is effective against a wide spectrum of both gram-positive and gram-negative organisms, including certain that are resistant to streptomycin.

Neomycin is poorly absorbed from the gastroenteric tract. For this reason, it has found use as an antibacterial agent in the bowel. It is said that some impurity in the neomycin preparation inhibits the growth of monilia in the bowel, and that for this reason neomycin, as an intestinal antiseptic, is superior to oxytetracycline and chlortetracycline. The oral dose of neomycin sulfate ranges from 0.5 to 1.0 Gm., given once every hour, for four hours. Side effects after oral use are not common unless the above doses are greatly exceeded.

The drug is amebacidal, but more information is needed on its specificity and possible toxicity before it can be used routinely.[37] A combination of neomycin and bacitracin was found effective for the treatment of human amebiasis by Felsenfeld, Kadison and Ishihara.[38] An adequate prothrombin level in the blood is essential in a patient who is receiving an antibiotic as a gastroenteric antiseptic and who subsequently is subjected to surgery. In such a patient the intravenous injection of vitamin K is advised to prevent a tendency toward postoperative bleeding.[24]

Kadison and others[39] gave the drug intramuscularly to 31 patients suffering from so-called virus pneumonia and tuberculosis and other diseases caused by gram-negative bacilli. Their results with neomycin are encouraging with the exception of far advanced cases of lung tuberculosis and brucellosis. Two other clinicians who used neomycin for the treatment of tuberculosis warn against its general use by stating: ". . . neomycin undoubtedly caused kidney and eighth nerve damage to a not insignificant number of patients."[40] Daily quantities of 7.5 to 10 mg. per kilogram of body weight, in divided doses, should not be exceeded if possible. Waksman and others[41] stated the following:

> Parenteral neomycin therapy should be undertaken only as a hospital procedure and should be accomplished by regular laboratory observation of renal and eighth nerve function. Treatment should be halted at the first indication of toxicity . . .

Ointments of neomycin (5 mg. per gram) have been used with success in

37. McVay, L. V., Jr., Laird, R. L., and Stern, T. N. Neomycin in the treatment of human amebiasis. Am. J. M. Sc. 223:20 Jan. 1952.

38. Felsenfeld, O., Kadison, E. R., and Ishihara, S. J. In vitro and in vivo tests with newer antibiotics against Endamoeba histolytica. Am. J. Pub. Health 41:1078 Sept. 1951.

39. Kadison, E. R., and others. Neomycin therapy; its use in virus pneumonia, tuberculosis and diseases caused by gram-negative bacteria. J.A.M.A. 145:1307 April 28, 1951.

40. Waisbren, B. A., and Spink, W. W. Clinical appraisal of neomycin. Ann. Int. Med. 33:1099 Nov. 1950.

41. Waksman, S. A., and others. Neomycin; nature, formation, isolation and practical application. New Brunswick, N. J., Rutgers University Press, 1953.

the treatment of impetigo, ecthyma, furunculosis and other types of cutaneous infection. Apparently sensitization and irritation due to the antibiotic or ointment bases are rare, but they have been observed and should be watched for. Another preparation for local use (Biomydrin Nasal Solution), which contains neomycin sulfate, gramicidin, phenylephrine hydrochloride, thonzylamine hydrochloride, and thonzonium bromide has been recommended as a nasal spray and nose drop. It is believed to be virtually free of the danger of sensitization.[42,43]

■ *Polymyxin B*

Polymyxin B sulfate (Aerosporin) has found use in the treatment of certain local, gastroenteric, urinary, meningeal and systemic infections caused by gram-negative bacilli. Absorption is negligible from the skin, gastroenteric or urinary tract. The drug has been recommended for prophylactic use; it rarely causes sensitization. Apparently it does not give rise to resistant strains.

For enteric infections, the drug is given orally (200 mg. per day). For the treatment of an infection of the urinary tract, it is instilled into the bladder or renal pelvis in saline (0.1 to 0.5 per cent) solutions. For topical application, solutions or ointments containing 0.1 to 1.0 per cent have been employed. The intramuscular dose of polymyxin B ranges from 1.5 to 2.5 mg. per kilogram per day, given in divided doses at 4 to 8 hour intervals.

Pain at the site of an injection may be minimized by using a solution of procaine for dissolving the drug. Other side effects which may be noted after intramuscular therapy, and particularly in patients over 60 years of age, include paresthesia, dizziness and weakness. Patients with renal impairment excrete the drug more slowly, hence smaller doses are needed to maintain an adequate blood level.

Beckman[25] stated as follows:

> Polymyxin has not been given widespread distribution, principally because of its renal toxicity. However, under controlled conditions with daily determinations of urinary output, blood urea nitrogen and urinary albumin, it appears possible to use it without undue risk. Indeed, Schoenbach and his group at Johns Hopkins found that in most instances albuminuria was transitory and that evidence of more severe kidney damage was limited to patients with preexisting renal impairment.

■ *Chlortetracycline, Oxytetracycline and Tetracycline*

Chlortetracycline was introduced as Aureomycin; oxytetracycline as Terramycin. The latest addition to the group is tetracycline. Chemically and pharmacologically they are all very closely related. Their outstanding characteristics are effectiveness in the treatment of mixed gram-positive and gram-negative bacterial infections, and absorption from the gastroenteric tract to a sufficient degree to make them useful for oral medication.

The oral administration of these drugs is most important. They are also available for local therapy, but because of their irritant action they are not to be given intramuscularly or subcutaneously.

42. Busia, S. N., and Friedman, L. L. An evaluation of topical antibiotic therapy in the local treatment of infections of the nose and sinuses. Antibiotics & Chemother. 3:299 March 1953.

43. Cohen, B. M., and Mendelsohn, R. Topical therapy of disturbances of the upper respiratory tract. Laryngoscope 63: 1118 Nov. 1953.

They may be injected intravenously, but only in true emergencies.

CHLORTETRACYCLINE—Optimal doses have not yet been established for this antibiotic. Before deciding on a dosage, the following should be given consideration: Too large a dose does not result only in loss of fecal excretion, but also in an increased frequency of side reactions. In this respect this and other broad spectrum antibiotics differ from penicillin. Secondly, an oral dose exceeding 250 mg. fails to produce a proportionately higher level in the blood.

The dosages used today are far below those recommended only a few years ago. Four 250 mg. doses per day or less are adequate to provide a satisfactory blood level in most patients. Each portion is to be taken with or immediately after a meal or together with a bland drink, preferably milk, buttermilk or yoghurt.[44] The drug should not be taken with aluminum hydroxide gel.[45, 46] Chlortetracycline for local use is available in ointments, solutions, dental pastes, surgical powders and so forth.

Because of the wide use and application of chlortetracycline, the discussion will be limited to the use of this drug by the oral surgeon. Oral administration of this antibiotic may be employed before, during and after any operative procedure. McEntegart and Porterfield in a report cited by the Lederle Company demonstrated that 54 of 200 patients had blood cultures positive for streptococci immediately after a dental extraction. As a rule, this postextraction bacteremia is harmless. In patients who suffer from heart disease, nephritis or diabetes, however, the extraction of a tooth may be dangerous since bacteria entering the systemic circulation may settle on damaged heart valves, multiply there and induce subacute bacterial endocarditis.

Jacobs,[47] therefore, considers it essential to prescribe chlortetracycline or penicillin prophylactically before tooth extraction in any patient with a history of rheumatic fever, valvular heart disease and so forth. He administers 250 mg. every four hours the day before, the day of and the day after dental extraction. Krasse and co-workers recommend local administration of chlortetracycline (a 15 mg. troche every six hours) as a prophylactic measure whenever a secondary infection is feared after any oral manipulative procedure.

Certain side reactions should be watched for. These include nausea, vomiting, looseness of stools, glossitis, stomatitis and skin eruptions. The prolonged oral use of chlortetracycline may lead to an overgrowth of nonsusceptible organisms, particularly monilia.

A recent article[48] called attention to reports that had appeared in France, describing a hitherto unrecognized complication of antibiotic therapy, namely a severe or fatal staphylococcal enterotoxemia caused by chlortetracycline and oxytetracycline. This article stated:

44. Hazards of broad-spectrum antibiotics. Lancet 1:967 May 8, 1954.

45. Technical note. University of Michigan Medical Bull. 16:51, 1950.

46. Di Gangi, F. E., and Rogers, C. H. Adsorption studies of aureomycin hydroxide on aluminum hydroxide gel. J. Am. Pharm. A. (Scient. Ed.) 38:646 Dec. 1949.

47. Jacobs, M. H. Chemotherapeutics and antibiotics in dentistry. Oral Surg., Oral Med. and Oral Path. 3:1247 Oct. 1950.

48. Stilwell, G. G. Fatal enterotoxic reactions caused by antibiotic therapy. Minnesota Med. 36:63 Jan. 1953.

It is now well recognized tha. the incidence of strains of *Micrococcus pyogenes* (Staphylococcus) that are resistant to antibiotics is increasing; at present more than 30 per cent of all strains of this organism are resistant to Terramycin and Aureomycin. If a patient who is receiving one of these antibiotic agents happens to have such a resistant type of *Micrococcus pyogenes* in his intestine, the stage is set for possible disaster.

The patient who harbors such an enterotoxic organism begins to vomit; extremely profuse watery diarrhea rapidly ensues, followed by hyperthermia, a decrease in blood pressure, anuria and uremia.

This syndrome is a true bacteriologic emergency. When diarrhea appears in a patient who is receiving Terramycin or Aureomycin, the physician should immediately prepare a smear of the stool and stain it by the ordinary Gram's method. If this syndrome is present, the slide will exhibit myriads of gram-positive cocci as practically the only organisms present.

. . . examination of the slide is sufficient to make the diagnosis and under no condition should the physician await the outcome of cultures before the method of treatment is changed.

If administration of these antibiotic agents is discontinued as soon as the syndrome appears, the number of coliform organisms rapidly returns to normal. . . . About two-thirds of patients treated in this fashion recover quickly; the remainder may die within a day or so. . . . The best treatment is to discontinue the administration of Terramycin or Aureomycin and begin use of erythromycin by mouth.

OXYTETRACYCLINE—The application of oxytetracycline is similar to that of chlortetracycline.

Osserman[49] reported on 231 patients who required various kinds of operative dentistry, treatment of infection or oral surgery. When the initial temperature was 100° F. or less, he initiated oral treatment by giving 250 mg. of oxytetracycline followed by an additional dose of 250 mg. every four hours. In more severe infections the first dose was equal to 500 mg. followed by 250 mg. every four hours. For prophylaxis and for the specific treatment of minor periodontal infections, he administered troches containing 15 mg. of the antibiotic or he applied an oxytetracycline paste or sterile oxytetracycline powder. Dental cones containing 5 mg. each, were also used in postextraction sockets.

Among Osserman's patients treated orally with oxytetracycline were 30 with cellulitis in whom it would normally have been necessary to establish drainage before surgical procedure. In two thirds of these patients fever was reduced to a normal temperature within 24 hours. Surgical procedure was then undertaken and completed. After surgical intervention, patients were maintained on oxytetracycline therapy for 48 hours. In another phase of the report Osserman discussed replacement of penicillin by oxytetracycline in patients with histories of cardiac disorders or rheumatic fever. On the second day after initiation of oxytetracycline therapy a tooth was extracted and ten minutes later a blood culture was made. Therapy was continued for another 48 hours. In not one of ten patients was there a positive culture 24 hours after surgery.

Schaffer[50] studied the use of oxytetracycline on 120 patients with 17 different conditions; 82.5 per cent of these responded "excellently" to oral oxytetracycline therapy. Nine patients showed side reactions. Nausea and diarrhea were noted

49. Osserman, H. A. Terramycin in dentistry. New York D. J. 18:509 Dec. 1952.

50. Schaffer, Julius. Clinical study of terramycin in dentistry. Oral Surg., Oral Med., & Oral Path. 6:965 Aug. 1953.

most frequently. When the drug was given in milk or with a teaspoonful of Coca-Cola extract, both nausea and diarrhea were controlled. Schaffer recommends oral administration of supplementary vitamins (especially B complex) for a period of five or more days in order to suppress lesions of the mucous membranes that can be produced by, or that may become infected with, Candida or other yeastlike organisms. He did not observe any signs of Candida but recommended, if they appear, cessation of treatment and the use of an alkaline mouthwash. Other authors recommending oral oxytetracycline therapy are Winter and Van Gaasbeek,[51] Pollock and Archer,[52] Di Conza[53] and Kelsten.[54]

According to Schaffer,[50] definite incompatibility exists between penicillin and oxytetracycline. He recommended that they should not be given together. He further recommended a change in antibiotic treatment if no favorable response is noted in 36 to 48 hours. A case of penicillin-oxytetracycline antagonism was also reported by Lane and others.[55]

Oxytetracycline is available for intramuscular use. Lane and his co-workers injected it intravenously into three patients suffering from cellulitis of the floor of the mouth. One patient received several doses of 500 mg. each. The authors recommended this kind of therapy for conditions in which oral therapy is impossible. Obviously, hospitalization is then necessary.

Conflicting reports have appeared in the literature on the effects of oxytetracycline on blood clotting. Vitamin K may be involved, since it is produced largely by bacteria in the intestinal tract. Additional information is required before a precise statement can be made on the relation of oxytetracycline, bacteria of the enteric tract, vitamin K and the clotting of blood. At present, the intravenous injection of vitamin K is advised if surgical procedure has been preceded by oral oxytetracycline therapy for a prolonged period of time.[24]

Only a few months ago Hay and McKenzie[56] reported that they had noted signs of toxicity in 8 per cent of 603 patients after oxytetracycline therapy. The authors did not include nausea, vomiting, heartburn, diarrhea and headache as signs or symptoms of toxicity since they had found it difficult to determine whether these symptoms had been due to the initial disease or had been induced by the antibiotic. They reported two fatalities. One of these had been a six year old physically well girl who had been a carrier of *Salmonella typhimurium* and had been treated for this reason with oxytetracycline. She had developed mild pyrexia, had vomited a little and had had "green" diarrhea on the morning of the fourth day of drug therapy. Treatment had been discontinued. That day her temperature was 102° F., and she had had 12 loose stools in 24 hours. The next morning she had developed intense circulatory failure and had died 24 hours after the onset of

51. Winter, Leo, and Van Gaasbeek, Bruce. Terramycin in oral surgery. New York D. J. 18:119 March 1952.

52. Pollock, S. L., and Archer, W. H. Clinical experience with terramycin in dentistry. Pennsylvania D. J. 20:10 March 1953.

53. Di Conza, P. J. Localized alveolar osteitis and terramycin. New York D. J. 19:518 Dec. 1953.

54. Kelsten, L. B. Root canal therapy for the primary teeth. New York J. Den. 24:123 March 1954.

55. Lane, S. L., and others. Terramycin in the treatment of cellulitis of the floor of the mouth. J. Oral Surg. 11:18 Jan. 1953.

56. Hay, P., and McKenzie, P. Side-effects of oxytetracycline therapy. Lancet 1:945 May 9, 1954.

diarrhea. Cultures made from throat, feces, enteric tract and lungs had revealed a pure growth of coagulase-positive *Staphylococcus aureus* which was sensitive to streptomycin and chloramphenicol but was resistant to penicillin, chlortetracycline and oxytetracycline.

Seven of their patients had developed a scarlatiniform rash with throat lesions on the fourth or fifth day of drug treatment. Five of these also had had diarrhea. In six of the seven patients a pure growth of coagulase-positive *Staph. aureus* had been obtained from throat swabs. Side effects noted in other patients included infections of the urinary tract in three patients, pyrexia in 24 patients and urticaria or transient erythema in 7 patients.

This report emphasized that oxytetracycline therapy is not without danger. It also emphasized that it is to the patient's advantage if he is treated with an antibiotic to which microorganisms are sensitive.

TETRACYCLINE—The drug tetracycline was developed from chlortetracycline by the removal of the chlorine atom from the molecule. The drug is new, and it will be some time before tetracycline is fully evaluated. The recommended oral dose ranges from one to six 250 mg. tablets per day, depending on body weight. Its indications are similar to those for oxytetracycline and chlortetracycline.

A few months ago Finland and coworkers[57] reported on a clinical trial with tetracycline. They had treated 118 patients, most of whom had had infections of the urinary or respiratory tract. They had found that the major clinical difference between tetracycline and its analogues was the distinctly lower incidence of gastroenteric symptoms. Tetracycline, however, is not free from side effects. Putnam, Hendricks and Welch[58] administered the drug (2 Gm. for three days) to 217 healthy men. Capsules were given to 111 and tablets to 106 subjects. Since the men were healthy, any symptoms relating to the gastroenteric tract were considered to be caused by the drug. Four of the 217 subjects exhibited what may have been an allergic response. It was necessary to withdraw the drug from two of these. Nausea, vomiting and diarrhea occurred in 5.5 per cent of the 217 men. Tablets were found to cause more minor side reactions than the capsules.

Very similar observations were recently reported in the *Lancet*.[59] Reference was made to 179 patients, 14, or almost 8 per cent, of whom had experienced discomfort varying from flatulence to nausea, vomiting and diarrhea. Ten of the 14 suffering from side effects had taken tetracycline (0.5 Gm. every six hours for four to ten days) as tablets, and four had taken the drug in capsules.[45]

Enterotoxic reactions have not been noted after tetracycline therapy. Caution, however, is in order. Welch[60] points out that noticeable differences exist in sensitivity of bacteria to tetracycline, oxytetra-

57. Finland, M., and others. Clinical and laboratory observations of a new antibiotic, tetracycline. J.A.M.A. 154:561 Feb. 13, 1954.

58. Putnam, L. E., Hendricks, F. D., and Welch, H. Tetracycline, a new antibiotic. (Abst.) J.A.M.A. 154:1129 March 27, 1954.

59. Letters to the editor. Antibiotic enterocolitis. Lancet 1:732 April 3, 1954.

60. Welch, H., and others. Bacterial spectrum of erythromycin, carbomycin, chloramphenicol, aureomycin, and terramycin. Antibiotics & Chemother. 2:693 Dec. 1952.

cycline and chlortetracycline. He worked with 250 strains of coagulase-positive staphylococci. His results emphasize again the importance of sensitivity studies before therapy; he further points out that substitution of one analogue for another may not accomplish the desired effect.[4]

■ *Chloramphenicol*

This antibiotic shares most of the properties of chlortetracycline, oxytetracycline and tetracycline. Like these drugs, it is particularly suited for oral administration, but it is also available in an ointment, as eye and ear drops and in ampules for intravenous use. Recently a repository Chloromycetin Intramuscular has been made available. According to the manufacturer, Parke, Davis and Company, this preparation is therapeutically effective over the same range of clinical entities which have been found to respond favorably to chloromycetin given by mouth. A dose of 1 Gm. every 8 to 12 hours is recommended for the treatment of a severe infection in an adult.

During recent years chloromycetin attracted much attention as a drug likely to cause agranulocytosis. Effects were noted in persons whose blood-forming tissues were presumably exceptionally susceptible, or in others who received this drug for a prolonged period of time. Since the onset of granulocytopenia is often rapid, it is recommended that chloromycetin therapy be associated with complete blood counts carried out at weekly intervals. Symptoms which should be indication for the discontinuation of therapy and for further blood studies include hemorrhage from the nose or other mucous membranes, unusually heavy menstrual loss, unexplained sore throat, or purpura.[61]

Recently, the antibiotics clinical trials committee of the British Medical Research Council sent questionnaires to various hospitals in order to survey the frequency of blood dsycrasias that had resulted from chloromycetin therapy. Twenty-eight cases of aplastic anemia and three cases of granulocytopenia were reported. In 24 of 31 patients, the doses administered had been in excess of, and the average had been over double that of, a dose calculated to be the necessary dose to control most infections. On the basis of this survey Hodgkinson[62] recommended that, without careful consideration of the risk involved, the dosage schedule should not exceed the following:

1. In adults, a total dose of 26 Gm.
2. In children, a total dose not to exceed the equivalent of 100 mg. per kilogram of body weight daily for seven days.
3. A period of treatment not to exceed ten days.

■ *Erythromycin*

The therapeutic indications of erythromycin resemble those of penicillin. Erythromycin is particularly effective against gram-positive cocci, but it possesses activity also against a few gram-negative rods as well as a few rickettsias and viruses. Of interest to the oral surgeon is the fact that pathological conditions such as septic sore throat, tonsillitis,

61. Annotations. Chloramphenicol and the blood. Lancet 2:122 July 19, 1952.

62. Hodgkinson, R. Blood dyscrasias associated with chloramphenicol. Lancet 1:285 Feb. 6, 1954.

pharyngitis and bronchitis have been treated successfully with this antibiotic.

Erythromycin is available for oral and cutaneous administration. Oral doses of 0.5 Gm. every six hours have produced satisfactory concentrations in the serum. In certain infections, such as pneumococcic pneumonia, a total daily dose of 0.6 Gm. has been found adequate. Enteric-coated tablets are preferable to capsules.[63,64] For pediatric use, erythromycin stearate is available as a suspension. One teaspoonful contains 100 mg. of the antibiotic. Thirty milligrams per kilogram per day in four or six doses is the amount recommended.[65] For topical application to the skin, erythromycin is available as an ointment.

Even though erythromycin resembles penicillin in its action, according to Jawetz as cited by Josselyn this antibiotic appears to belong in his Group 2 along with the so-called broad-spectrum antibiotics. Until contrary clinical evidence is presented, synergism, therefore, may be considered when this antibiotic is used in conjunction with oxytetracycline, chlortetracycline, chloramphenicol and tetracycline, but antagonism is to be suspected when erythromycin is used with penicillin, streptomycin, bacitracin, neomycin and polymyxin B.

Side effects, such as vomiting and diarrhea, have been noted occasionally after oral administration of erythromycin. These disappeared when medication was withheld. Patients subjected to prolonged erythromycin therapy should be observed carefully for possible signs of systemic toxicity. Due consideration must also be given to the possibility that bacteria acquire resistance to this antibiotic.

■ *Tyrothricin*

Tyrothricin (0.01 to 0.05 per cent in isotonic solution) effectively combats accessible gram-positive organisms on the skin, mucous membranes and possibly in bone cavities. In the form of throat lozenges (Tyrozets), it has been used for the treatment of gram-positive throat and mouth infections and after surgical procedure involving the oral cavity. Its toxicity when used systemically limits its use to topical application.

This antibiotic contains at least two active ingredients, gramicidin (10 to 20 per cent) and tyrocidine (40 to 30 per cent). Gramicidin is the active ingredient against gram-positive organisms; tyrocidine is active against those that are gram-negative. Gramicidin is the most important of the two; hence tyrothricin is particularly useful in dealing with infections containing primarily gram-positive organisms. Gram-negative organisms, when also present, may interfere. They contain cephalin and related substances which are strongly inhibitory for gramicidin. (Saliva, urine, red blood cells and serum have a slight inhibitory action.)

Tyrothricin is toxic when permitted to be absorbed; therefore, it should never be given intramuscularly or by mouth. Lozenges should not be chewed or swallowed. (Dogs, given lethal doses showed anoxia, hyperpyrexia, anemia, hematuria,

63. Robinson, H. M., Jr., and Cohen, M. M. Treatment of granuloma inguinale with erythromycin. J. Invest. Dermat. 20:407 June 1953.

64. Kirby, W. M. M., Maple, F. M., and O'Leary, B. Erythromycin serum concentrations following administration in acid-resistant tablets. Antibiotics & Chemother. 3:473 May 1953.

65. Sylvester, J. C., and Josselyn, L. E. Absorption of erythromycin. II. Erythromycin stearate. Antibiotics & Chemother. 3:390 Sept. 1953.

biliuria and micropathologic changes in all major organs.) Tyrothricin must never be applied as a dry powder; and as a solution, it should not be used in conjunction with benzalkonium chloride (Zephiran) and benzethonium chloride (Phemerol). Its local use must be restricted to the treatment of a region in which the agent can come in direct contact with susceptible microorganisms. Occasionally, surgical intervention is required before this kind of treatment can be effective.

Recently a broadly effective antifungal antibiotic, nystatin (Mycostatin, 250,000 units), was introduced. It is recommended for the prevention and treatment of intestinal moniliasis. It may be administered in combination with 250 mg. of tetracycline. Nystatin also may be given with other commonly used antibiotics for the prevention and treatment of infections of the lower intestine and anus caused by *Candida albicans*.[66]

■ *Summary*

The oral surgeon uses antibiotics for prophylaxis and for the treatment of infection. In the selection of an antibiotic, he is guided by the following:

1. Clinical experience.
2. Recommendations from the bacteriological laboratory.
3. A combination of factors which will make one antibiotic more suitable than another for a particular patient.

For prohpylaxis, one group of oral surgeons will continue to favor penicillin, and if penicillin sensitivity exists, members of this group will give some consideration to erythromycin. The other group will favor one of the broad-spectrum antibiotics, such as oxytetracycline, chlortetracycline or tetracycline. In patients with a history of diseases of the heart, kidneys and pancreas, prophylactic treatment is a must if surgery involves tooth extraction or a similar procedure.

If the surgeon finds himself treating an acute infection, he will be wise to base his initial antibiotic therapy on examination of a smear prepared from a specimen of exudate taken by aspiration or obtained after incision. An additional specimen or blood sample taken for culture and bacterial sensitivity studies will tell him the following day that his initial antibiotic therapy was correct, or that a change should be made.

In patients requiring treatment of a chronic infection, it is recommended not to initiate antibiotic therapy until the results of a carefully conducted bacteriological analysis have become available. In established infections mixtures of organisms are usually present, not only at the surface but also in the deeper tissues. Antibiotics, therefore, must be administered so that they will reach offending microorganisms in sufficient concentration. Practically always, systemic therapy (intramuscular or oral) accomplishes this more effectively and with a lower incidence of side effects than local treatment.

Medication for "local" use is a misnomer, for the oral cavity (or the skin) offers an excellent opportunity for absorption, and for local and systemic sensitization, as well as for the growth of nonsusceptible organisms. Under conditions as yet unknown, bacteria acquire resistance all too frequently, hence for minor

66. New concept in antibiotic therapy. Squibb, E. R. & Sons. A-5109 Nov. 1954.

cuts and bruises, antibiotics should never be used.

Each of the antibiotics is capable of inducing undesirable effects.

The use of an intradermal skin test will effectively single out the individual who is seriously allergic to penicillin. According to Flipse, the ratio of severe reactors is 10 per cent of the population in southern Florida.[28] This, he believes, is due to the fact that penicillin is air-borne in Florida. Obviously, penicillin should be administered to a penicillin sensitive patient only in an emergency, when no other drug is expected to be life-saving, and then only with proper precautionary measures. In any patient, penicillin therapy should be discontinued immediately if signs appear suggesting anaphylactoid-type effects. Oral penicillin therapy must be considered, at this time, as a relatively safe and effective procedure, but nearly all new drugs or modes of drug administration are generally considered safe, until proved otherwise. Caution, therefore, continues to be in order.

After intramuscular injection of bacitracin, side effects (albuminuria and pain at site of injection) can be expected in one third of patients. Obviously, this type of medication should be reserved for infections by organisms which are not susceptible to other antibiotics. Neomycin and polymyxin should be employed with similar reservations. Sensitization or cutaneous moniliasis has apparently not been observed after local application of these antibiotics.

Chlortetracycline and oxytetracycline are reported to have been responsible for the production of severe or fatal staphylococcal enterotoxemia. Apparently, this complication is increasing, or it is increasingly recognized. It occurs in a patient who is receiving one of these drugs and who happens to harbor a resistant type of *Micrococcus pyogenes*. Appearance of a profuse watery diarrhea, hyperthermia and vomiting should induce the surgeon to prepare immediately a smear of the stool and stain it by Gram's method. In the presence of this syndrome, the slide will show myriads of gram-positive cocci. According to Stilwell, chlortetracycline or oxytetracycline medication is to be discontinued immediately, and therapy should be continued with erythromycin by mouth.

Tetracycline is the newcomer to this group of broad-spectrum antibiotics. It has produced fewer side effects than chlortetracycline or oxytetracycline; however, it is not free from undesirable symptoms. Side effects relating to the gastroenteric tract were noted in 5 per cent of normal men who were given this drug.

Nausea, vomiting and diarrhea can be reduced or eliminated in a patient receiving one of the broad-spectrum antibiotics by mouth if such a drug is taken after a meal, or in conjunction with yoghurt, buttermilk, milk, carboxymethylcellulose or possibly with an extract of Coca-Cola. Supplementary administration of vitamin B is indicated whenever a dose of 2 Gm. of any one of these drugs is given for more than five days. The intravenous injection of vitamin K is advised if major surgery was preceded by oral administration of an antibiotic as a gastroenteric antiseptic.

Erythromycin induces vomiting and diarrhea in an occasional patient, but over-

growth of nonsusceptible organisms has apparently not been observed.

Streptomycin and particularly dihydrostreptomycin (intramuscularly) may induce vestibular damage, renal complications and sensitization.

Chloramphenicol medication should be accompanied by the determination of complete blood cell counts at weekly intervals. Discontinuation of this drug is indicated with the appearance of hemorrhages from the nose or other mucous membranes, an unusually heavy mentrual loss, or an unexplained sore throat if associated with granulocytopenia or anemia.

Because of its toxicity when used systemically, the use of tyrothricin should be restricted to local application. Use of this antibiotic in a troche or lozenge is not generally recommended.

Traumatic injuries of the temporomandibular joint

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The derangements of the temporomandibular joint that are produced by traumatic injuries may be classified as follows:

Acute derangements: (1) undisplaced condylar fractures, (2) displaced condylar fractures that are not dislocated, (3) condylar fracture dislocations, (4) joint strains and contusions, (5) acute dislocations.

Chronic derangements: (1) postfracture condylar syndrome,[1] (2) posttraumatic painful joint, (3) recurrent dislocation and subluxation.

For the purpose of convenience, these derangements will be discussed in groups so far as is possible rather than by individual topics, since most injuries present group problems rather than individual ones. It should be remembered, however, that each patient presents a separate clinical problem and should be managed as an individual.

The opinions or assertions contained in this article are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

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1. Markowitz, H. A., and Gerry, R. G. Temporomandibular joint disease. Oral Surg., Oral Med. & Oral Path. 2:1309 Oct. 1949; 3:75 Jan. 1950.

■ *Traumatic Derangements and Their Treatment*

CONDYLAR FRACTURES—In their review of the 662 fractures of the mandible received by military personnel in the Korean war, Chipps, Canham and Makel[2] pointed out that only 67 cases involved fracture of one or both mandibular condyles, or about 10 per cent. In noncombatant circles this ratio increases directly with the incidence of vehicular accidents and fistic encounters. When condylar fracture is present and the condylar, or proximal, fragment is not displaced, reduction and immobilization of the remainder of the mandible in its anatomic position will produce satisfactory union of the condylar fracture. It is mandatory in the treatment of these uncomplicated fractures, as in the treatment of any temporomandibular injury, that the clinician follow the patient's progress long enough to determine that he has normal function of the healed condyle, unless such function is anatomically impossible. The criteria for evaluating normal condylar function on this basis are: (1) roentgenographic evidence of normal condylar excursion, (2) ability of patient to masticate normally with teeth on opposite side, (3) ability of patient to depress the mandible normally without deviation toward the side of the injured condyle.

Ordinarily normal condylar excursion will recur spontaneously, but if it does not, all available indicated methods of encouraging normal excursion such as physiotherapy, exercises, and training devices should be used until maximum function has been obtained.

It has already been mentioned that when undisplaced condylar fracture occurs, the mandible should be immobilized with teeth in occlusion until clinical union takes place. This is especially true in patients who are bedridden because of concurrent injuries. Frequently in these instances, especially in bicondylar fractures, the entire distal fragment, which includes the body of the mandible, will drift posteriorly, and repair occurs with the mandible in this position. The result is facial deformity and derangement of occlusion. Immobilization of the distal fragment is essential even in edentulous patients. In such instances, the mandible can be retained in its anatomic position easily by passing a Steinmann pin through the anterior portion of the mandible and fastening it to a plaster head cap with rubber band traction (Fig. 1, left).

DISPLACED CONDYLAR FRACTURE IN WHICH CONDYLAR FRAGMENT IS NOT DISLOCATED—Ordinarily, in fractures, three types of displacement exist. They are as follows:

1. A medial inclination of the proximal or condylar fragment that has resulted from the medial pull of the external pterygoid muscle. The articular eminence has prevented anterior displacement or dislocation of the condylar fragment (Fig. 1, right).

2. Overriding of the fractured end of the condylar fragment either medial or lateral to the mandibular ramus. In such cases the articular surface of the condyle remains within the glenoid fossa, but the space between the articular surface of the

2. Chipps, J. E.; Canham, R. G., and Makel, H. P. Intermediate treatment of maxillofacial injuries. U. S. Armed Forces M. J. 4:951 July 1953.

condyle and the roof of the glenoid fossa is increased (Fig. 1, right).

3. Bicondylar fractures in which the remainder of the mandible has either been forced or has drifted posteriorly. In the latter type of displacement there is considerable malocclusion of teeth typified by an acquired distal occlusion (Fig. 2, left). The deformities in these instances can be corrected readily by intermaxillary fixation of the teeth in anatomic occlusion. As stated earlier, if the patient is edentulous a pin is passed across the mandibular symphysis, and rubber band traction to a plaster head cap is used to pull the mandible anteriorly into a normal anatomic relationship.

The first two types of displacement present the greater problem. Some writers advise that most displaced condylar fractures be restored to anatomic position by means of open reduction.[3] Other authorities feel that open reduction of these fractures is rarely indicated.[4,5] It has been my experience, however, in displacements of this type, that if the remainder of the mandible can be reduced and immobilized in an anatomic position, provided the length of the external pterygoid muscle has not been significantly shortened by anterior displacement of the condylar fragment, normal condylar function will eventuate even though considerable dis-

3. Becker, A. B. Condylar fractures. Oral Surg., Oral Med. & Oral Path. 5:1282 Dec. 1952.
4. Parker, D. B. Personal communication.
5. Lane, S. T. Personal communication.

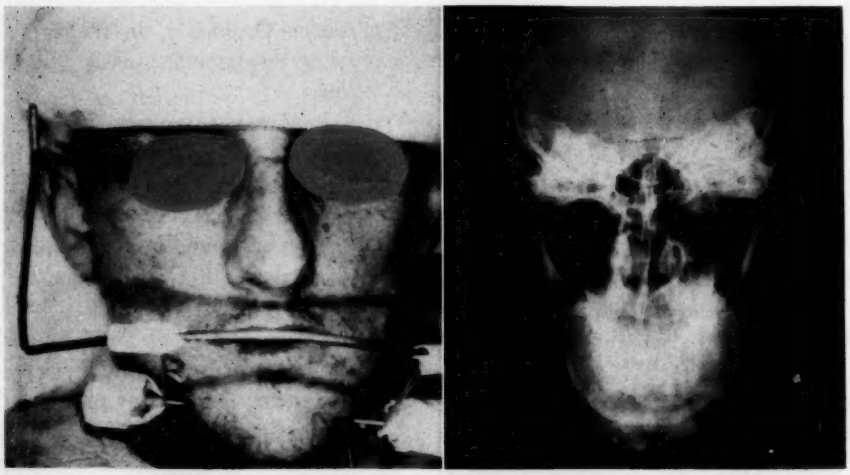

Fig. 1—Left: Bicondylar fractures in almost edentulous patient. Stainless steel pin has been passed through mental protuberance to immobilize symphysis fracture. Rubber band traction from pin to traction frame keeps mandible from dropping posteriorly. Right: Displaced condylar fracture without dislocation. Condyle has been displaced medially and overriding of proximal fragment has occurred. Surgical interference is not indicated here; normal joint function will eventuate after healing is complete. (Photography by Morton Russin)

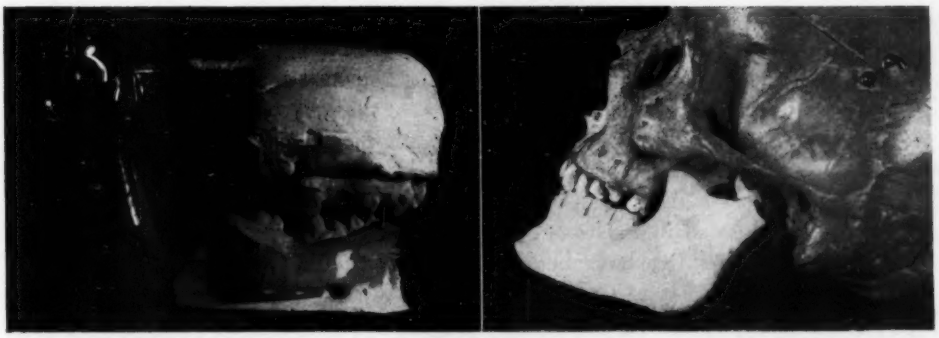

Fig. 2—Left: Models showing posterior displacement of mandible in bedridden patient with untreated bicondylar fractures. Right: Skull showing fracture-dislocated condyle. Condyle has been pulled into infratemporal fossa by spastic contraction of external pterygoid muscle

placement exists. This observation has been confirmed by Waldron.[6]

CONDYLAR FRACTURE DISLOCATION—Fracture dislocation is the condition which exists when the fractured condylar fragment is displaced anteriorly, usually medially, to the crest of the articular tubercle or into the infratemporal fossa (Fig. 2, right). Fractures of this type usually take place when the traumatic impact occurs at the moment that the mandible is depressed and the condyle is at the crest of the articular eminence. In such instances the spastic contraction of the external pterygoid muscle either holds the condyle at the crest of the articular eminence or pulls it toward its origin, and consequently into the infratemporal fossa.

If such a fracture is allowed to heal without reduction, a hematoma usually will form and fill the space between the glenoid fossa and the posterior surface of the fracture-dislocated condyle. In the process of organization, dense cicatricial adhesions will form. In addition, the stretched articular disk will limit anterior mobility of the displaced condyle after healing. The condylar mobility, after the fracture has repaired, is further reduced as a result of the extreme shortening of the external pterygoid muscle because its insertion into the anterior surface of the condyle has moved anteriorly and medially close to its origin. After healing, the mandible will deviate toward the injured side during depression, and the patient will be unable to masticate with the teeth on the opposite side.

Usually, a fracture-dislocated condyle that has healed in malposition can be expected to function only as a hinge type joint. In general, the greater the displacement of the fracture-dislocated condyle, the greater the residual limitation of the mandibular motion. Such limitation is undesirable because the patient finds it necessary to masticate with the teeth on

6. Year book of dentistry, 1953-1954 series. Chicago, Year Book Publishers, 1954, p. 285-286.

the injured side, using the opposite uninjured condyle which will ultimately develop hypermobility. Because this resultant hypermobility of the uninjured condyle usually does not become annoying for months, or even for a year or two after the fracture, it is referred to as the postfracture condylar syndrome.[1]

In those instances in which there is bicondylar fracture dislocation, the postfracture condylar syndrome is not a cause for concern, since the deforming forces are similar in both joints, and the patient will be forced to work out a usable system of bilateral mastication. Fortunately, osteoarthritis does not develop in badly displaced condylar fractures as it does in a fracture in the weight-bearing joints.

If the fracture dislocation exists in only one condyle, three systems of treatment are available: (1) immobilization without reduction, (2) open surgical reduction and (3) condylectomy.

Immobilization Without Reduction—If immobilization of the mandible is done without open reduction, the teeth are kept in anatomic occlusion. No attempt is made to reduce the condylar fragment or to replace it in the glenoid fossa. In such instances it usually is necessary to train the patient so that the deformed joint may function efficiently after healing has occurred. This training is accomplished through exercises based on limitation of motion of the normal condyle and stimulation of motion of the deformed condyle. The simplest exercise that can be used for this purpose requires no special equipment. The patient is instructed to place the tip of his tongue against the lingual surfaces of the molar teeth on the side of the normal condyle. He then opens and closes his mouth from this position, which stimulates deviation of the mandible away from the side of the injured condyle (Fig. 3, above left). The patient usually repeats this procedure for ten minutes hourly during the day until he is able to masticate easily with the teeth on the unaffected side. In many instances there is sufficient condylar excursion (3 or 4 mm.) to accomplish this, but there is insufficient condylar excursion for unconscious, undeviating mandibular depression. This condition will not produce a postfracture condylar syndrome so long as the patient has comfortable bilateral mastication.

Simple training devices also are useful in retraining the fracture-dislocated condyle. These devices consist of a flanged appliance to stimulate movement away from the deformed condyle for the patient with natural teeth (Fig. 3, above right), and a maxillary denture with an inclined plane on the palate to encourage mastication on the side of the uninjured condyle for the edentulous patient (Fig. 3, below). Active assistive exercises may be used when there is insufficient incisal opening. It is often desirable that these procedures be carried on concurrently with physiotherapeutic treatment and short wave diathermy.

Open Surgical Reduction—In some instances of fracture dislocation of the mandibular condyle, the proximal fragment can be replaced by depressing the molar teeth on the side of the injured condyle with a bite-block and simultaneously elevating the condyle back into the glenoid fossa with a sharp elevator. This

procedure is simple but usually is ineffective and, therefore, is not attempted ordinarily. According to Thoma,[7] Sleeper,[8] Becker,[3] and Markowitz and Gerry,[1] reduction of the fracture-dislocated mandibular condyle usually requires surgical exposure of the articulation, recovery of the displaced condyle from the infratemporal fossa, and its replacement into the glenoid fossa in its normal position.

I have observed that menisectomy usually is necessary to the recovery and replacement of the fracture-dislocated condyle. If there are no other mandibular fractures on the side of the injured condyle, transosseous fixation need not be used. The mandible is immobilized in occlusion, and the injury is treated as an uncomplicated subcondylar fracture (Fig. 4). If other mandibular fractures are present and there is insufficient occlusal support, transosseous wiring is indicated to prevent medial or lateral displacement of the body of the mandible with resultant malocclusion (Fig. 5).

After the subcondylar fracture treated

7. Thoma, K. H. Oral surgery. St. Louis, C. V. Mosby Co., 1948, p. 632.

8. Sleeper, E. L. Open reduction of condylar fractures. Oral Surg., Oral Med. & Oral Path. 5:4 Jan. 1952.

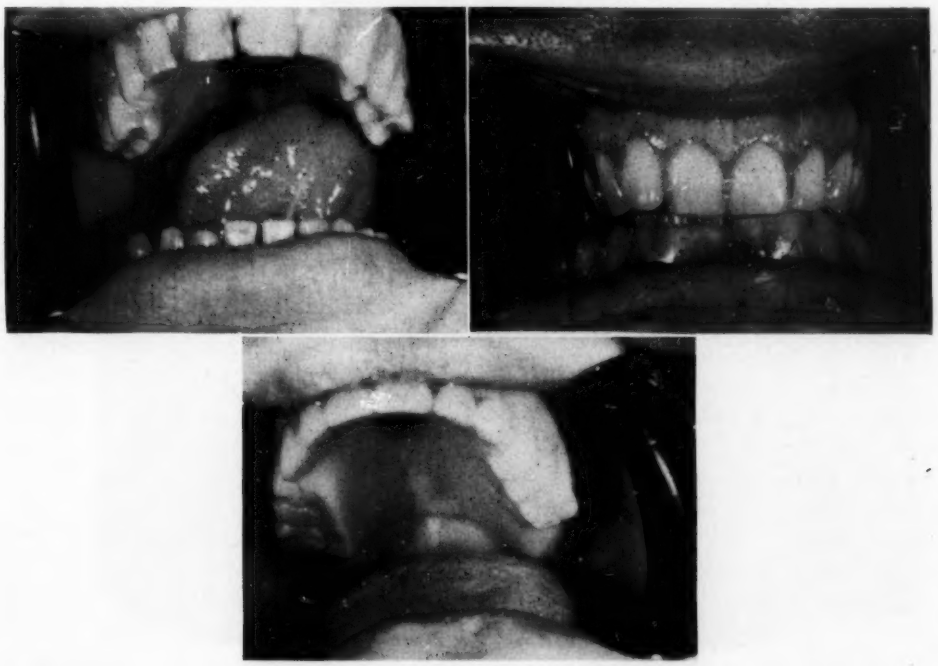

Fig. 3—Above left: Tongue exercise to encourage unilateral excursion of mandible and anterior excursion of opposite condyle. Above right: Flanged appliance to encourage unilateral excursion of mandible and anterior excursion of opposite condyle. Below: Palatal inclined plane on full denture to encourage unilateral mandibular excursion and anterior excursion of opposite condyle in edentulous patient

in this manner has healed, there usually is considerable limitation of motion because of scarring. This condition may respond to the same follow-up routine as was discussed earlier for the healed unreduced fracture dislocation. The principal difference is that when recovery is complete, the patient has an essentially anatomic joint. If there is sufficient scarring, however, adequate condylar excursion may never be obtained, and the injured joint may function only as a hinge.

Condylectomy—This procedure[9] is used infrequently, usually in instances in which open reduction has been attempted

9. Smith, A. E., and Robinson, M. New surgical procedure in bilateral reconstruction of condyles, utilizing iliac bone grafts and creation of new joints by means of non-electrolytic metal. Preliminary report. Plast. & Reconst. Surg. 9:393 May 1952.

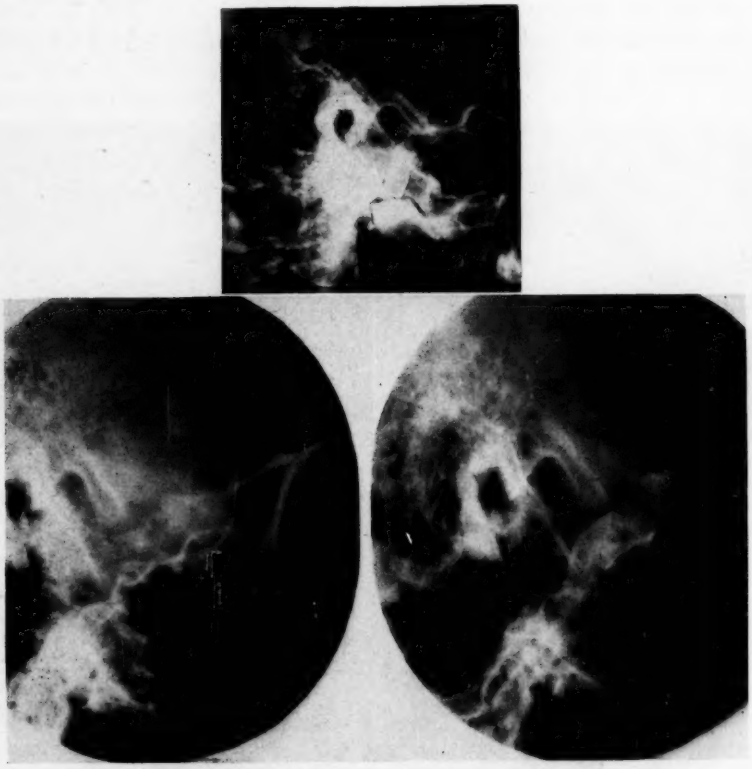

Fig. 4—Above: Closed position of recently fractured condyle; anterior displacement approaches dislocation. Open reduction was performed. If there had been less anterior displacement, open reduction would not have been indicated. Below: Same condyle (closed and open views), one year postoperatively. Full range of condylar excursion has returned and patient has healthy anatomically functioning joint

Fig. 5—Above: Tomogram showing fracture-dislocated condyle; condyle displaced into infratemporal fossa. Concurrent fractures of coronoid process, visible on plate, and of symphysis are present. Below: Anatomic result of open reduction. Surgery necessary in this instance since fragments could not be reduced into anatomic occlusion without reducing condylar fracture. Patient did not develop completely normal range of condylar motion although he was able to masticate with teeth on opposite side

unsuccessfully or in healed unreduced fracture dislocations in which symptoms are present. These patients require a period of immobilization with the mandible in anatomic occlusion, and also require the same type of retraining as has been described earlier.

Although these patients can be taught to masticate bilaterally, there usually is a deviation of the mandible toward the condylectomized side during unconscious mandibular depression, as a result of the destruction of the insertion of the external pterygoid muscle. When the fracture dislocation is severe, however, patients in whom a condylectomy has been performed may have better final function and a shorter postoperative course than those in whom open reduction has been performed.

DISCUSSION—In any comparison of the three methods of management of the fracture-dislocated condyle, it seems evident that the first two are the treatments of choice, and that condylectomy should be reserved for special circumstances. Immobilization without reduction is indicated in instances where the anterior displacement is minimum, and open reduction is indicated where this deformity is more extensive. The clinician must rely on his own judgment in the planning of treatment of the several intermediary displacements. In cases of doubt, it has been my policy to withhold surgery until heal-

ing has occurred and there has been an opportunity to re-evaluate the patient after his retraining procedures have been completed.

Patients who have had open reduction done, as already mentioned, require more time to attain normal mandibular function, but usually in these instances there has been more deformity to begin with. It is unlikely that these patients would have done as well if open reduction had not been performed. One patient with minimum fracture dislocation on whom open reduction was performed had good union and a very effective range of condylar excursion a year and a half after surgery. In fact, his range of condylar excursion was so extensive that it almost approached hypermobility (Fig. 4).

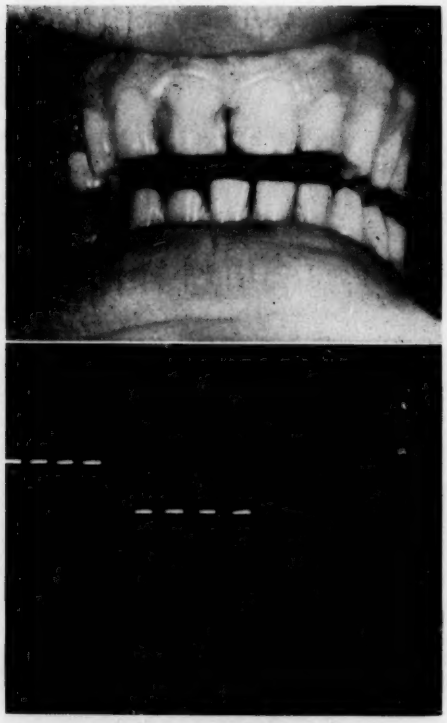

Fig. 6—Above: Showing range of lateral excursion of mandible away from side on which condylectomy had been performed. There is a range of 4 to 5 mm., sufficient to insure bilateral mastication. Below: Acute dislocation. Chronic dislocation would present same roentgenographic findings

Open reduction or condylectomy should not be performed lightly. Of the last 100 mandibular fractures treated at the U. S. Naval Hospital, St. Albans, N. Y., only two open reductions of fracture-dislocated condyles have been performed. One patient was treated postoperatively who had had a fracture dislocation treated by unilateral condylectomy at another hospital. Evaluation of his record indicated that open reduction had been attempted, but that the fracture-dislocated condyle had been stripped of its blood supply and was therefore removed. The patient was transferred to St. Albans two weeks postoperatively, and after undergoing the usual routine of training, was able to masticate efficiently and had no residual symptoms except for a slight deviation toward the condylectomized side during unconscious mandibular depression (Fig. 6, above). He was ready for discharge much sooner than other patients who had been treated in the usual manner.

Early condylectomy may be the treatment of choice in condylar fracture dislocations, especially if the displacement is great. By this method, the interference of the stretched articular disk and that of the displaced condyle is eliminated entirely, and the effect of residual scarring is largely reduced.

Fractures of the head of the radius

are routinely treated by the removal of the head and there is no interference with normal joint function. A suggestion of this sort may be considered as radical, but evaluation of treatment results in our own patients who had had severe fracture dislocations, as well as evaluation of results seen in patients from other institutions who have later come under our observation, indicates conclusively that fixation without reduction or open reduction is not successful in the management of severely dislocated, unilateral condylar fractures. Early condylectomy with postoperative retraining may well be the most effective form of management, and may be used more and more frequently in the future. In support of this conjecture, Campbell, White and Anderson[10] reported an instance of prolonged bilateral dislocation of the mandible that had been treated by bilateral condylectomy; in this instance, the patient had satisfactory function and no acquired malocclusion nine months after surgery. On the other hand, Smith and Robinson[9] reported an instance in which bilateral condylectomy had been performed after severe mandibular fractures, and stated that after eight weeks of mandibular immobilization, the mandible drifted 5 mm. into retrusion within a few hours after mandibular mobilization. Constant elastic traction was then maintained for eight months. In this instance, the immediate result was good, but after 16 years the patient developed mandibular retrusion with open bite. I am of the opinion that a similar deformity would not result after unilateral condylectomy, but I have had limited experience in this field.

In the case described earlier, the fact that the patient was able to masticate with the teeth of the opposite side indicates sufficient residual capacity to protrude the mandible to prevent significant deviation toward the condylectomized side when the teeth were in occlusion. It should be emphasized again, however, that routine condylectomy should not be performed in all cases of severe fracture dislocation of the mandibular condyle. It is only suggested that in those instances in which the displacement is severe and open reduction has been performed, if the condyle appears to have been so badly traumatized or so extensively stripped of its blood supply that repair of the fracture appears to be definitely in jeopardy, condylectomy might be a feasible alternative treatment. Time alone will establish whether surgery of this type is warranted.

It should be re-emphasized, as stated earlier, that bilateral fracture dislocation does not require surgical exposure of the joint if the teeth can be reduced into anatomic occlusion. In these instances the periarticular and articular deformities are similar on both sides and the patient usually will work out an individual, but nevertheless satisfactory, type of masticatory function. In all cases of fracture dislocation, because of concurrent edema, hematoma, and dense scarring after repair, body section roentgenography should be utilized (Fig. 5). If roentgenographic evaluation of this type is not possible, 35 degree angulation from below seems to be satisfactory (Fig. 4, below).

JOINT STRAIN AND CONTUSION—Joint strain and contusion are considered to-

10. Campbell, J.; White, T. C., and Anderson, H. Case of bilateral dislocation of mandible of nine months duration. D. Record 72:230 Oct. 1952.

gether because frequently their symptoms are similar, even though the forces that produce the condition are different. Contusion is less severe, occurs less frequently and is the result of direct compressive trauma to the joint. It is characterized by pain, edema, limitation of motion, and mandibular deviation toward the injured condyle. Contusion does not occur as a result of transmitted force to the temporomandibular joint—for example, by a blow to the mental protuberance—as the spastic external pterygoid muscle is an excellent shock absorber.

Joint strain is the result of a "stretching" force that has caused extension or even rupture of the fibers of the capsule and is characterized by essentially the same symptoms as contusion. Strain may be severe when the mandible is traumatized at another point and there is luxation, without fracture, of the condyle. Hematoma of the articular and periarticular tissues, with subsequent scarring, may occur in both strain and contusion.

Joint strain is the painful condition that accompanies acute dislocation or disk derangement. Contusions rarely cause residual symptoms and usually respond well to local heat, diathermy and, if observed early, to local injections of hyaluronidase. Strains, especially if the hemorrhage is severe, may produce considerable scarring with subsequent painful limitation of motion. This is the same process that occurs after the healing of malposed subcondylar fractures and is known as "posttraumatic painful joint."[1] It responds well to guided exercises instituted to restore normal function, to local heat and to physiotherapy as has already been described.

The acute strain itself is well treated by mandibular immobilization. This is instituted to prevent secondary hemorrhage and to permit repair. Immobilization is particularly useful after strain that has accompanied acute derangement of the disk since the scar tissue formed helps to provide future limitation of the condylar hypermobility that primarily produced the strain.

ACUTE AND CHRONIC DISLOCATION—Acute and chronic dislocations have been included under traumatic derangements as they certainly are responsible for traumatic injuries to the joint. However, they are rarely, if ever, the result of an outside force. Even the acute dislocation caused by yawning or exodontic procedures is almost invariably secondary to the existence of chronic condylar hypermobility of which the patient frequently is unaware. In this instance, the patient acquires the muscular capacity to move the condyle sufficiently anteriorly so that the articular surfaces of the joint no longer are in contact, and the obliquely inclined posterior aspect of the anteriorly inclined condyle permits it to be elevated into the infratemporal fossa (Fig. 6, below).

Acute dislocation produces severe strain and should be treated by reduction and immobilization for two to three weeks in order to prevent secondary hemorrhage with additional hematoma and to permit tissue repair. In such instances the existence of a temporary posttraumatic painful joint is almost an asset, since the patient will alter the motion habits which produced the primary hypermobility. When chronic dislocation is accompanied by strain, it should be treated as an acute

dislocation. When concurrent strain does not occur, immobilization is of little or no therapeutic value. After cessation of the acute symptoms, the causative hypermobility must be controlled or the dislocation will recur.

■ *Conclusions*

In general, the fundamental effect of external trauma to the temporomandibular joint is the limitation of condylar motion. Hypermobility of the uninjured condyle may occur as a result of trauma, as a part of the postfracture condylar syndrome.

Open reduction of condylar fractures is indicated only when there is severe fracture dislocation, or when it is impossible to reduce the teeth into correct anatomic occlusion. In very severe fracture dislocations, condylectomy may be the treatment of choice. This technic may be used increasingly in the future.

Corrective exercise is an important adjunct in the treatment of traumatic joint derangements, and patients who have been so injured cannot be regarded as cured until such time as normal function of the mandible has been achieved.

■ THE FURTHERANCE OF SCIENCE

To foster research of immediate practical value at the cost of exploratory research has consequences not unlike the squandering of natural resources. Both impair the welfare of future generations. We who have benefited so richly from the discoveries of our predecessors have an obligation to our successors. As scientists we can fulfill that obligation by pushing forward our explorations on the frontiers of knowledge, for the achievement of material objectives, as did Pasteur, or merely in the quest for knowledge, as did Faraday.

Too great emphasis on research that is of present value has a harmful influence on the education of scientists. It encourages training for immediate useful service at the expense of education which is a foundation for continued intellectual growth and ultimate competence to solve unanticipated problems of the future. It fosters undue specialization.

If those who support science think the goal of science to be quick answers to practical questions, scientists will be trained for limited objectives. As society accepts the responsibility for supporting more scientists, more men and women will be recruited who are content to fit themselves for a small sphere of scientific action. There is useful work for them to do, and organized research will undoubtedly increase their usefulness. But if the quality of scientific training is determined by the needs of those who are content to be mere technicians, those who would be more will suffer.—*Detlev W. Bronk, "The Role of Scientists in the Furtherance of Science," Science 119:225 February 19, 1954.*

Extraction wound healing: clinical observations

■ *W. Howard Davis, D.D.S.; Adrian O. Hubbell, D.D.S.; William E. Bogart, D.D.S., and Van M. Graves, D.D.S., Long Beach, Calif.*

Many writers have stated that the blood clot is conducive to normal healing of extraction wounds.[1-17] Clinical studies[18-35] have indicated that some dressings improve the healing of lower molar wounds. Experimental studies[36,37] have indicated that most dressings do not slow the initial organization of a clot. Large tightly packed dressings, however, if maintained, apparently delay final healing.[38] The displacement by the dressing of the central portion of a large clot has been credited with elimination of that portion of the clot which may break down before organization of the clot can occur. It appears that by this means some extensive wounds are influenced to heal as smaller wounds.

Although the role played by systemic[39-42] and local[39,43] factors has been emphasized, the antibacterial effect of suitable dressings is assumed to account for the balance of improvement noted after the use of dressings as reported in studies of these problems.[19]

There appears to be little agreement in the dental profession regarding the value of socket dressings. There is, however, a preponderance of evidence that a blood clot alone is not sufficient in lower molar sockets, especially in wounds caused by the extraction of lower third molars. A small but consistent percentage of these wounds heal in such a manner as to require local sedative dressings and narcotizing medication. Such medication is necessary if the patients are to be kept comfortable for some portion of the healing period.

1. Bloom, D. Misuse of sulfonamide compounds. Arch. Dermat. & Syph. 49:249 April 1944.

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5. American Medical Association, Council on Pharmacy and Chemistry. Sulfonamides for local application deleted from N.N.R. J.A.M.A. 137:157 Sept. 20, 1947.

6. Dent, Ben. Sulfanilamide—treatment of oral lesions by local application. D. Digest 46:137 April 1940.

7. Devine, J. C. Use of allantoin and sulfanilamide ointment in extraction sockets and oral surgery. D. Digest 50:267 June 1944.

8. Elwell, K. R. New approach to treatment of dry sockets. J.A.D.A. 31:615 May 1944.

9. Gottlieb, B., and Crawford, H. M. Therapy and prophylaxis of dry sockets. Am. J. Orthodont. & Oral Surg. (Oral Surg. Sect.) 29.328 June 1943.

10. Krashen, A. S. Preliminary report on the use of sulfanilamide in the average extraction case. J.A.D.A. 27:1199 Aug. 1940.

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12. Olech, Eli. Value of implantation of certain chemotherapeutic agents in sockets of impacted lower third molars. J.A.D.A. 46:154 Feb. 1953.

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16. Russell, L. T., Jr. Comparison in methods of prevention of local alveolar osteitis. Am. J. Orthodont. & Oral Surg. (Oral Surg. Sect.) 30:95 Feb. 1944.

17. Versnel, J. C. Healing of extraction wounds after introduction of hemostatics and antibiotics. J.A.D.A. 46:146 Feb. 1953.

18. Allen, L. J., Sulphonamides and penicillin therapy as adjuncts in oral surgery. New York J. Den. 16:145 April 1946.

19. Archer, W. Harry. Analysis of 226 cases of alveclalgia. D. Rays 12:1 Nov. 1936.

In the study to be described, those wounds classed as "complicated healing" were sockets in which there was no infection of soft tissues or abnormal swelling present, but were, rather, normal appearing though painful in healing. In this series only two of the classical dry sockets were encountered that were completely bare, septic, extremely painful and slow in healing. The occasional dry socket must be recognized as a problem, but the greater number of sockets that can be classified as "complicated healing" makes them a more important clinical problem.

■ *Purpose and Method of Study*

The purpose of the study herein described was to attempt to evaluate clinically oxytetracycline (Terramycin) cones and sulfa cones as socket dressings. The Council on Dental Therapeutics[44] has indicated that there has been a lack of controls in the studies of socket medications reported prior to 1942. In the present study, an attempt was made to obtain figures from a control group which could be added to the figures already recorded.[19, 45]

Punch card records were kept of the condition of 3,000 lower molar sockets. No medication was used in the first 1,000 sockets, and they were considered as controls. The second 1,000 sockets were treated with sulfa (5 grain sulfanilamide, 5 grain sulfathiazol) cones. The third 1,000 were treated with oxytetracycline (5 mg.) cones. The patient's ages were recorded in decades, as well as the sex, preoperative and postoperative antibiotic medication, the presence of acute or chronic infection, postoperative course, and the dressing used. Each unit recorded represented a tooth extracted. Only the information on lower molar sockets was used as these sockets are the most frequent site of "complicated healing." One antibiotic cone was placed in each root socket, and three cones were used in larger third molar sockets. Cotton gauze

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28. Levy, A. T. Improvement on the procedure of topical application of the sulfa drugs. J.A.D.A. 30:1045 July 1943.

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37 Hubbell, A. O., and Austin, L. T. Extraction wounds and therapeutic agents: an experimental study. J.A.D.A. 28:251 Feb. 1941.

38. Christopher, R. F. Histological study of healing in relation to the extraction of teeth. (Abst.) Northwest. Univ. Bul. 43:5 Dec. 7, 1942.

39. Eman, V. H. Dry socket problem. J. Oral Surg. 2:158 April 1944.

40. Gardner, B. S. Postoperative considerations regarding extraction of teeth. J.A.D.A. 16:235 Feb. 1929.

41. Osterloh, J. P. Thiamine hydrochloride in treatment of dry sockets. J.A.D.A. 29:1445 Aug. 1, 1942.

42. Whitfield, A. J. Use of thiamine chloride in prevention of pain from dry sockets. J.A.D.A. 28:450 March 1941.

43. Podolin, M. Etiology, prediction and treatment of dry sockets. D. Cosmos 78:1038 Oct. 1936.

44. Ostrander, F. D., and Hartman, F. W. Local use of sulfonamides. J.A.D.A. 29:1051 June 1942.

45. Krogh, H. W. Incidence of dry socket. J.A.D.A. & D. Cosmos 24:1829 Nov. 1937.

Table 1

Number of instances of "complicated healing" in 2,874 extractions

Type of tooth extracted	No dressing			Sulfa cones			Oxytetracycline cones		
	Total extracted	Complicated healing		Total extracted	Complicated healing		Total extracted	Complicated healing	
		No.	%		No.	%		No.	%
Lower first molar	205	10	4.87	201	10	5.0	187	5	2.68
Lower second molar	333	10	3.0	310	11	3.55	307	3	.98
Lower third molar	454	59	13.0	433	44	10.3	444	26	5.85
Erupted	237	19	8.0	259	20	7.72	200	6	3.0
Partially impacted	112	16	14.3	90	12	13.35	104	7	6.73
Completely impacted	105	24	22.9	84	12	14.3	140	13	9.3

packs were placed over all sockets for approximately ten minutes after each extraction. Thiopental sodium anesthesia was used for all the extractions.

■ *Postoperative Course*

The patients were seen three days after extraction had been performed. They were asked if they had experienced much pain, and if so when. If the pain had occurred after the extraction but was decreasing by the third day, normal healing was assumed. If pain was present and increasing on the third day, the wounds were classified as "complicated healing."

There was a noticeable consistency in each of the three groups with regard to the percentages classified as instances of "complicated healing" between the first, second and third molars (Table 1). This indicates that sufficient numbers were included in the survey to make it reliable. Krogh[45] has reported on a large series of cases in which no medication was used. In Table 2 the controls in this study are compared with the cases reported by Krogh. There is a striking similarity in the observations made of the condition of the sockets of the first, second and third molars (as a group).

The sockets of the completely impacted third molars showed the greatest benefit from medication. In the control group, 22.9 per cent had instances of

Table 2

Observations made in control group compared with observations reported by Krogh

Type of tooth extracted	Krogh 1937—controls			No dressing		
	Total extracted	Complicated healing		Total extracted	Complicated healing	
		No.	%		No.	%
Lower first molar	453	19	4.2	205	10	4.87
Lower second molar	460	23	5.0	333	10	3.0
Lower third molar	601	75	12.5	454	59	13.0

"complicated healing." When the sulfa cones were used, there was a 38 per cent decrease with only 14.3 per cent painful sockets. The oxytetracycline cones produced still greater benefits (60 per cent decrease), 9.3 per cent being reported as "complicated healing."

Parenteral antibiotics used postoperatively did not alter healing significantly. There were not enough patients who had received preoperative parenteral antibiotic therapy to permit any evaluation of its effect on healing.

There were no significant differences between the age groups in the percentage of sockets classified as "complicated healing." There was only one instance in which an allergy was suspected and that was in the group that had been given sulfa cones. The reaction consisted of a mild rash. Because of the difficulty of clinically evaluating healing time, no statistical evaluation was made. There appeared to be no difference in the completed healing time between the three groups. There were no instances of foreign body reaction. Occasionally fragments of both sulfa and oxytetracycline cones could be seen if the sockets were irrigated after three days.

■ *Summary*

A study was made of 2,874 lower third molar extractions. No medication was used for one third of the wounds and these were considered as controls. Sulfa cones were used in one third of the cases, and oxytetracycline (Terramycin) cones in the final third. Appearance and subjective symptoms were recorded for the instances of normal healing and "complicated healing." Only two instances of the classical dry socket were observed.

In the series in which sulfa cones were used, there was a decrease in wounds classified as "complicated healing" when compared with the control group. In completely impacted third molar wounds in which sulfa cones were used, there were 38 per cent fewer "complicated healing" sockets than in the control group.

Oxytetracycline cones showed a beneficial effect consistently. In completely impacted third molar wounds in which oxytetracycline cones were used, there were 60 per cent fewer painful sockets than in the control group.

No adverse reactions were noted to the sulfa or oxytetracycline cones either systemically or locally.—*123 Atlantic Avenue.*

■ SOURCE OF SUPPLY

Behind all your political applications, there is a region of intellectual action to which practical men have rarely contributed, but from which they draw all their supplies. Cut them off from this region, and they become eventually helpless. *John Tyndall, "Lectures on Light."*

VOLUME 13 • JULY 1955 • NUMBER 3 CASE REPORTS

Garré's osteomyelitis of the mandible: *report of case*

■ *Glenn J. Pell,* D.D.S.; William G. Shafer,† D.D.S.; G. Thaddeus Gregory,‡ D.D.S.; Ronald S. Ping,§ D.D.S., and Lewis B. Spear,|| D.D.S., Indianapolis*

In 1893, Carl Garré described a lesion of bone characterized by focal gross thickening of the periosteum with peripheral reactive bone formation resulting from a mild irritation or infection.[1] This lesion, then, represented an atypical reaction of bone to a mild chronic osteomyelitis, and it is from this reaction that the entity derived its name, Garré's nonsuppurative, sclerosing osteitis or osteomyelitis. Since the original description of this lesion, it has come to be well recognized by the orthopedic surgeon and pathologist. Clinically, it occurs most commonly in young persons, before the age of 25, most frequently involves the anterior surface of the tibia, and may or may not regress without surgical intervention. Roentgenographically, it appears as a focal overgrowth of bone on the outer surface of the cortex, occasionally described as a "reduplication" of this cortical layer of bone. Histologically, the lesion consists of newly formed bone and osteoid tissue showing a mild chronic inflammatory reaction of the fibrous interstitial connective tissue.

Because there is far greater opportunity for infection to enter the bone of the maxilla and mandible than any other bone in the body, it is surprising that this sclerosing, nonsuppurative osteomyelitis has not been described more frequently in the dental literature in this country. It is possible that this reaction is commonly seen clinically, but that it has not been recognized as being analogous to the lesions seen elsewhere.

In the past there has been a common tendency for both dentists and physicians to treat the jaws as a part separate from the rest of the organism and to consider the various disease processes which take place therein as being unique in character. This is an unfortunate failing. Though there are certain anatomic features characteristic of this region, it should be recognized and emphasized that all fundamental pathologic phenomena which affect the human body are identical, regardless of where they occur.

In 1948, Berger reported a case of "perimandibular ossification"[2] which exhibited all of the characteristic features of Garré's osteomyelitis. Since the dental literature contains only a few references to this entity, the following case is reported in an attempt to point out that such a reaction is not limited to the long bones and that it probably occurs more frequently in

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||Chairman, and professor of oral roentgenology.

1. Garré, C. Ueber besondere Formen und folgezustande der akuten Infektiosen, Osteomyelitis. Beitr. z. klin. Chir. 10:241, 1893.

2. Berger, A. Perimandibular ossification of possible traumatic origin: report of case. J. Oral Surg. 6:353 Oct. 1948.

the jaws than was formerly believed, the scarcity of reported cases being due to the lack of recognition.

EXAMINATION—A 14 year old negro boy entered the University of Indiana Dental Clinic on January 4, 1954, with a chief complaint of pain in the left side of the mandible and a swelling of the outer surface of the body of the mandible on the left side in the bicuspid and molar region (Fig. 1, left). He stated the condition had been present approximately one month.

Intraoral examination revealed a deeply carious lower left first molar. In addition, the swelling of the mandible which was noticeable externally could also be seen opposite the molar teeth. This swelling was bony hard to palpation. In the lateral jaw roentgenogram, considerable periapical involvement of the carious first molar was revealed (Fig. 1, center). In the occlusal view, a large bony swelling that measured approximately 6 cm. in anteroposterior dimension and 1.3 cm. in its outward projection could be seen on the outer surface of the body of the mandible (Fig. 1, right). The bony mass appeared to be well calcified and exhibited rather regular trabeculation. The outer surface of the mass was smooth in outline and appeared to show a thin but definite cortical layer.

In addition a small break in the continuity of the normal outer cortical plate of the mandible could be noted, slightly distal to the first molar.

DIAGNOSIS AND TREATMENT—Because of the unusual nature of this lesion and the suspicion that it was probably related to the carious molar, this tooth was extracted and the granulomatous tissue thoroughly removed. At the same time, a flap of tissue in the mucobuccal fold was reflected and a biopsy taken from the bony mass.

Histologic examination of the removed bone revealed much young reactive new bone formation with considerable osteoid tissue present associated with proliferating osteoblasts (Fig. 2). The interstitial tissue was more fibrous in nature than usual and exhibited a diffuse infiltration of a moderate number of lymphocytes and plasma cells. The diagnosis was Garré's nonsuppurative sclerosing osteomyelitis.

Fig. 1—Left: View of patient taken January 12, 1954 showing swelling of mandible on left side. Center: Lateral roentgenogram taken January 8; carious first molar and periapical involvement are evident. Right: Occlusal view taken January 8 showing bony outgrowth of mandible

POSTOPERATIVE COURSE—The patient experienced no postoperative difficulties; he has been followed periodically since that time. Occlusal roentgenograms taken at his return visits exhibit regression of the bony mass as evidenced by an obvious decrease in the magnitude of its outward projection (Fig. 3). The patient also states that the mass has definitely decreased in size. At the time of his last visit, June 4, 1954, the mass measured approximately 0.7 cm. in its outward projection. It was noted, however, that although the mass appeared to be regressing, it was also becoming more dense, roentgenographically, with more definite trabeculation (Fig. 4).

DISCUSSION—The case described represents an example of one type of reaction of bone to infection which, although not common, is seen with enough frequency in other parts of the body to warrant emphasis of its occurrence in the jaws. Because severe carious destruction of the teeth with ensuing infection of the bone is seen so frequently in young children, it is amazing that this type of reaction does not occur much more frequently.

The age of the patient apparently plays a role in the type of reaction that can be expected of infected bone. Bone of young individuals obviously reacts in a much more dynamic fashion than that of older individuals. The nature of the infection or the virulence of the infecting organisms are undoubtedly of major importance in determining whether the process is to be an osteolytic or an osteoblastic one. It is important to recognize that this lesion is a destructive one in its early stages and that the cortical bone is perforated in the same manner as it is in the early development of a fistula. However, at this point the destructive process apparently becomes attenuated, so that instead of continuing to the usual suppurative periosteitis and subsequent perforation of the overlying soft tissues and oral mucosa or skin, the infectious process stimulates this periosteum with the result already described.

The basic reaction to mild infection as described here is not unusual; the atypical feature is the site of the reaction: the periosteum. The dentist is familiar with a lesion which occurs within the jaw, one that has a similar

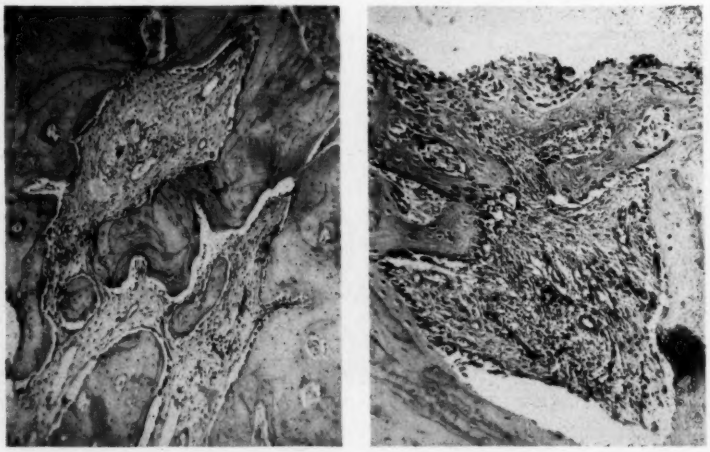

Fig. 2—Photomicrographs through two different views of biopsy specimen showing reactive new bone formation with noticeable osteoblastic activity and fibrous type of marrow infiltrated by small numbers of chronic inflammatory cells

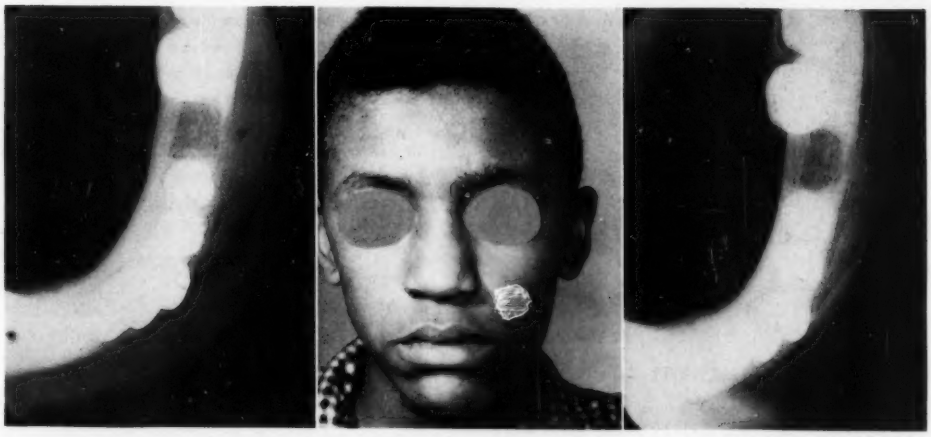

Fig. 3—Left: Occlusal roentgenogram taken February 24; reduction in size of growth after extraction of first molar may be noted. Center: View of patient taken April 14; swelling of mandible is noticeably decreased; asymmetry not pronounced. Right: Occlusal view taken April 14; further reduction in size of growth is evident

etiology and is classified under several different names, depending on the circumstances. Condensing osteitis, which is frequently seen involving the periapical bone around carious teeth with pulpal involvement in young persons, is a process identical in its fundamental nature except that the proliferation of bone is of endosteal origin rather than periosteal. Similarly, the diffuse radiopaque lesions occasionally noted in edentulous regions are etiologically and pathogenetically similar, albeit, they are frequently seen in older individuals. Another lesion, possibly of a similar nature but considerably more obscure in origin, is the so-called cementoma or periapical osteofibroma.

The regression of the lesion in Garré's osteitis is a somewhat unusual feature, but it merely serves to point out the ability of the jaws to be remodeled after deformation and be restored to their original contour. The role of muscle attachments, movement, and so forth, is not thoroughly understood; undoubtedly, however, they contribute to this reformation which grossly may be likened to the remodeling of a callus after fracture.

When a differential diagnosis is made, it is well to remember that another lesion that occasionally involves the jaws may present a similar roentgenographic picture; namely,

Fig. 4—Occlusal roentgenogram taken June 4 showing considerable reduction in size of outgrowth of mandibular bone. The bone is also becoming somewhat more dense

Ewing's sarcoma. This neoplasm also occurs in younger individuals, and since it presents a similar appearance, great care must be taken in distinguishing between the two because of the extremely serious nature of this latter disease.

SUMMARY—A report of a lesion of the mandible has been presented which is clinically, roentgenographically and histologically identical with a lesion that occurs in other bones of the skeleton that has been classified as Garré's nonsuppurative sclerosing osteomyelitis. It is believed that this case represents an example of the same entity, and that this condition probably develops more frequently in the jaw than has been thought previously.

Avulsion of peripheral nerves for trigeminal neuralgia: *report of case*

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This case illustrates a palliative, surgical approach to peripheral nerves involved in a trigeminal neuralgia. The method described is often neglected in the literature.

The patient, a 71 year old white woman, complained of a "terrible tic douloureux." One year prior to admission at University Hospital, Ann Arbor, Mich., the patient had experienced a series of lancinating, excruciating pains in the left infraorbital region. The attacks had lasted over a period of two days and had left a residual soreness in the region.

Two months later the attacks had returned and had been accompanied by similar sensations in the mental foramen region on the left side. Two subsequent episodes of pain had ensued, with the most recent beginning a week prior to admission. During the last attack the pain had persisted almost constantly in the distribution of the left infraorbital and mental nerves with only a matter of minutes between paroxysms. No relief was afforded by position, applications of heat or cold or sedative drugs. The attacks were brought on either by cutaneous touch to the left cheek or by masticatory movements.

The patient was referred to the oral surgery service by the neurosurgery service of the hospital in November 1952, for avulsion of the afflicted peripheral nerves.

PAST HISTORY—The patient had been a dressmaker since the death of her husband 11 years previously. There were no significant abnormalities in the family, health, or social histories.

EXAMINATION AND TREATMENT—The patient was alert, intelligent and cooperative. There were no significantly abnormal facies or habitus. Clinical and roentgenographic examinations disclosed an edentulous mouth without prosthetic rehabilitation. It was not possible to incite a paroxysm of pain, but the letter of referral to the hospital, the note of referral from the neurosurgery service and the patient's emphatic statements provided all the

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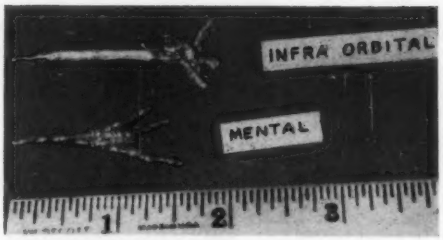
assurance needed to believe the pains had been a fact.

The impression gained from the examination and history was that the patient had major trifacial neuralgia in the second and third divisions on the left side.

Avulsion of the infraorbital and mental nerves on the left side of the head through intraoral approaches was the treatment of choice.



Peripheral nerves removed by avulsion technic. Left, proximal segments removed from bony canals. Right, peripheral segments removed from soft tissues

COURSE—The day after the examination the patient received adequate sedative and analgesic medications. In a sterile manner the operative sites were infiltrated with 2 per cent procaine with 1:50,000 epinephrine.

The following procedure was employed for both nerves. An incision was made in the mucobuccal fold. The overlying facial musculature was elevated and thus the nerve was exposed. Procaine solution was injected directly into the nerve, which was then grasped with a hemostat. By slow, firm, steady traction the nerves were avulsed from the infraorbital and mental foramens (illustration). After the nerves separated from their proximal segments, the procedure was repeated with the peripheral segments that had innervated the soft tissues. The mucoperiosteal flaps were replaced and sutured in position with interrupted black silk sutures.

After a six month period there has been no recurrence of the neuralgic pain and no disability aside from persistent anesthesia in the regions normally innervated by the infraorbital and mental nerves.

COMMENT—The various kinds of treatment of trigeminal neuralgia may be classified as palliative and radical. Palliative procedures affording temporary relief, but not a cure, include sectioning, avulsion and injection of a long-lasting anesthetic or a sclerosing solution into the peripheral nerves. Radical treatment consists of trigeminal rhizotomy or retrogasserian neurotomy which effects permanent relief in 94 per cent of the cases treated, according to one series.[1] The palliative approach is not advocated to replace the radical procedure or vice versa, but the two should supplement one another.

Indications for the palliative procedures, as enumerated by Grantham and Segerberg,[2] are as follows:

1. For patients who are poor surgical risks and in whom craniotomy would be hazardous.

2. For instances of differential diagnosis between atypical facial neuralgia and major trigeminal neuralgia.

3. For patients "who state that had they comprehended the way facial anesthesia would be, they would not have submitted to a trigeminal rhizotomy."[2] This complaint is less apt to occur if a palliative procedure is instituted first and is followed by a permanent procedure if pain recurs.

The use of alcohol injection frequently is accompanied by intense pain and results in a high percentage of unsuccessful attempts with an occasional untoward complication of facial or extraocular paralysis.[2] By contrast, the avulsion technic is a precise, effective method of providing a longer period of relief than obtained with injection of alcohol.

1. Peet, M. M., and Schneider, R. C. Trigeminal neuralgia. J. Neurosurg. 9:367 July 1952.

2. Grantham, E. G., and Segerberg, L. H. Evaluation of palliative surgical procedures in trigeminal neuralgia. J. Neurosurg. 9:390 July 1952.

Osteogenic sarcoma of the mandible: *report of case*

■ *Charles A. Resch, D.D.S., Cleveland*

Localized hypertrophy of the alveolar bones of the jaws is found frequently in dental practice since supporting dental structures subjected to abnormal stress usually respond by a physiologic hypertrophy. Treatment is usually conservative, with removal of the bony mass by reduction to give ridge conformity. Response usually is satisfactory.[1] Thoma[2] has stated that osteogenic sarcoma is a rare disease; a review of the literature of the last decade revealed ten reports. Dechaume and Baclesse,[3] reporting a case of osteogenic sarcoma of the left side of the mandible of a man, discussed in detail the difficulties of roentgenographic and histologic diagnosis. The tumor they described was reported as being an osteoma in three consecutive histologic studies. These authors believed, however, that it was an osteogenic sarcoma from the onset.

REPORT OF CASE—A 48 year old housewife was first seen at the Cleveland Clinic in December 1948. Her chief complaint was a localized painless swelling of the anterior portion of the mandible of five months' duration. There was no history of trauma. She had been under medical care elsewhere for pernicious anemia for a period of ten months.

Examination revealed a hard, nodular enlargement of the anterior portion of the mandible that extended both labially and lingually in the incisor region. The teeth in the section were viable and firm but in slight labial malalignment, which condition the patient believed to be progressive. The overlying mucosa was intact, with localized erythema, but without noticeable vascular engorgement.

Roentgenograms revealed an osteoporosity of septal bone and a loss of lamina dura, with thickening of the periodontal space limited to the central incisor and right lateral incisor region (Fig. 1).

Blood studies, including phosphorus, calcium and phosphatase, were all within normal range except for a slightly elevated blood sugar which was 186 mg. per 100 cc. Blood pressure was 150/90 mm. The clinical impression was that it was fibrous dysplasia.

OPERATION—The patient was operated on in January 1949, one month after her initial examination. The procedure consisted of stripping back the gingival mucosa, reducing the bony swelling with an osteotome, and resecting the hard bony mass piecemeal. The five remaining lower teeth plus the four incisors were removed.

Microscopic study of the excised tissue which included nine teeth and 12 small, bony tissue fragments revealed that the tissue formed by bone was well differentiated with evenly distributed nuclei, broad bony trabeculations and, in some areas, zones of fibrous tissue (Fig. 2, left). Examination of one of several subsequent sections revealed a small spicule of well formed bone adjoined by osteoid tissue of somewhat atypical configuration but without tumor giant cells or undue cellularity (Fig. 2, right). One tooth was adjoined by a newly formed, well differentiated bone. The pathologist's report was osteoma of the mandible.

Postoperatively, the oral condition was satisfactory, although there was some edema.

Department of dental surgery, Cleveland Clinic, and the Frank E. Bunts Educational Institute.

1. Rosedale, R. S., and Hargraves, W. B. Osteoma of mandible; report of massive tumor. J.A.D.A. 29:942 June 1942.

2. Thoma, K. H. Clinical pathology of the jaws. Springfield, Ill., Charles C Thomas, 1934, p. 643.

3. Dechaume, M., and Baclesse, F. Ostéosarcome du maxillaire inférieur; difficulté du diagnostic radiographique et du diagnostic histologique. Presse méd. 59:387 March 28, 1951.

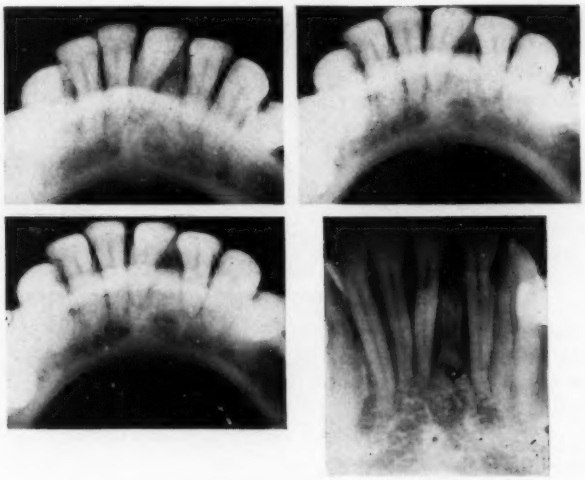


Fig. 1—Roentgenograms showing osteoporosity of septal bone and loss of lamina dura with thickening of periodontal space, limited to central incisor and right lateral incisor region

The patient had a low-grade fever (99.8° F.) with perspiration and hot flashes. A medical consultation revealed normal findings in regard to the heart, lungs, abdomen, and the extremities. The medical impression was menopausal syndrome. She was discharged on the second postoperative day.

The patient was observed again two weeks later. At this time there was considerable inflammatory reaction over the anterior lingual region that was confined principally to the gingival margin. Exposed bone was noted along the ridge crest. Pain was present, but there was no suppuration. Roentgenograms again revealed

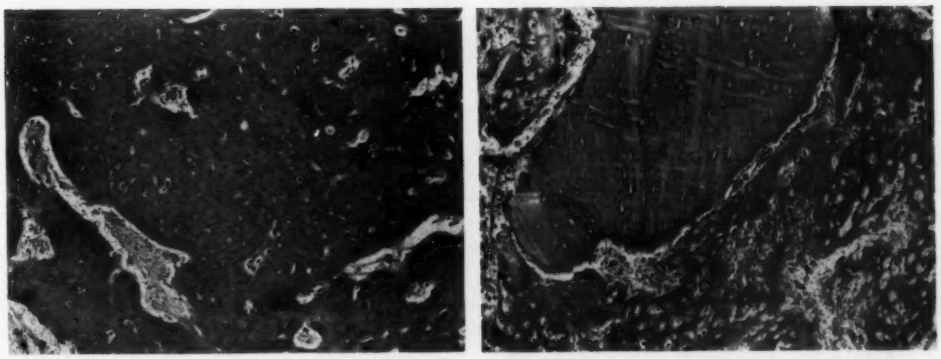


Fig. 2—Left: Broad zone of dense bone with evenly distributed nuclei and small patches of fibrous stroma. Right: Osteoid tissue of atypical character about bone spicule of normal type

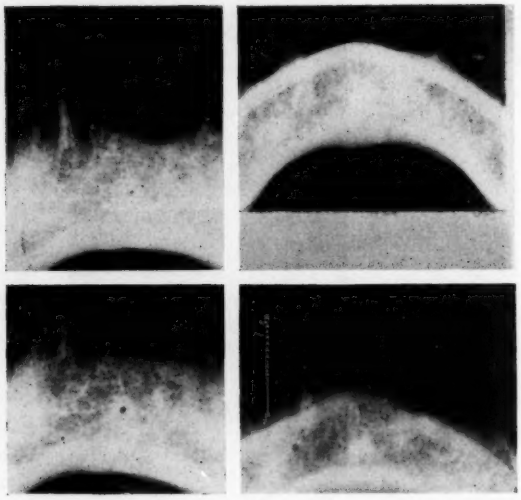


Fig. 3—Above: Sequestration in mandible. Below: Cavitation after exfoliation of sequestrum

an osteoporosity with developing sequestration (Fig. 3, above).

An occlusal roentgenogram revealed several small exostoses along the labial margin, but the cortical bone plates were apparently intact. Blood studies showed: hemoglobin 12.0 mg. per 100 cc.; white blood cell count, 2,750 with 70 per cent neutrophils, 1 per cent eosinophils, 29 per cent lymphocytes, and the blood sugar 116 mg. per 100 cc., four and three-quarter hours postprandial.

When the patient was next examined 21 days later (February 24, 1949), the inflammatory reaction had subsided slightly, but the lingual margin still appeared inflamed and edematous. The patient reported that a large section of bone had spontaneously exfoliated two weeks previously with minimal reaction. The temperature was 98.6° F. A roentgenogram revealed bone loss with cavitation (Fig. 3, below).

The patient was observed twice during the following month (March), at which times the healing progress appeared to be satisfactory. Prosthetic construction was contemplated.

One and a half months later (May 19, 1949) the patient returned and complained of a uniform, hard, painless enlargement of the anterior portion of the mandible between the mental foramens, which involved both labial and lingual surfaces. There was no associated lip numbness. The overlying mucosa appeared normal with the exception of congested blood vessels on the labial aspect. The patient had been aware of the lesion within the previous four-week period. The occlusal roentgenogram revealed an increased sclerosis of the medullary portion of the anterior mandible with slight labial proliferation of the cortical layer. The patient complained of increasing nervous tension and loss of endurance.

The physical examination at this time showed the blood pressure to be 170 per 100 mm. Hg. The blood calcium was elevated to 13 mg. per 100 cc. and the blood phosphorus was 3.2 mg. per 100 cc. A Sulkowitch's test was negative. The patient was advised to consider resection of this part of the mandible. Thirteen days later, under local anesthesia, a biopsy specimen was obtained from both the labial and lingual aspects of the region.

The microscopic examination revealed this tissue to be formed mostly by dense, bony or osteoid tissue but with foci of considerable cellularity (Fig. 4, left). The latter zones were formed by cells of medium size, round, poly-

hedral or spindle-shaped and sometimes arranged along the irregular margins of osteoid tissue (Fig. 4, right). There were occasional mitoses present and rarely an atypical mitosis. A rare multinucleated giant cell was present. Dense fibrous tissue adjoined the neoplasm. In areas in the bony portion there were diffuse zones of necrosis. The pathologist's report was sclerosing osteosarcoma.

The patient was admitted to the hospital 16 days later, and the anterior portion of the mandible was resected by George Crile, Jr., M.D., and Clifford L. Kiehn, M.D., D.D.S. A stainless steel wire was inserted between the fragments of the mandible. The gross specimen consisted of a segment of bone and soft tissue with over-all measurement of 3.4 by 3 by 2 cm. The bone segment was flat and measured 3.4 by 1.2 by 1.1 cm. It was adjoined by a soft, reddish tissue mass. On one surface there was a zone of glistening mucous membrane. Margins of resection of bone revealed a red cancellous marrow. Sections taken longitudinally through the specimen showed a central zone of hard, gray-white tissue replacing the marrow in the gingival half of the specimen, the white area extending to within 3 mm. of one line of resection and within 5 mm. of the other line of resection. The soft tissue was formed principally by striated muscle, but in the gingival aspect there was an irregular zone of hard to quite firm white tissue, 8 mm. in thickness and 15.5 mm. in width, immediately adjoining the bony cortex and the white tissue within the bone. Normal muscle appeared to be present marginally. Sections made after decalcification revealed an irregular white area near the gingival aspect that was 1.2 cm. in width and that extended to within approximately 1 mm. of the line of resection on the right side. The soft tissue mass was larger than in previous sections and appeared to extend to within 2 mm. of the line of excision although a portion of it was characteristic of scar tissue. The inferior half of the specimen was formed by dense cortical bone and red cancellous bone.

The postoperative sequence proved uneventful. The patient continued to be depressed but was discharged on the eighth postoperative day.

She was followed closely for the next two months. Her chief complaint was pain which was controlled by mild sedation. On August 30, approximately two months after the operation, the healing appeared complete. There was no weight loss.

On September 20, three months after the resection, there was a recurrence of the tumor that was evidenced by enlargement of the terminal segment of the right side of the

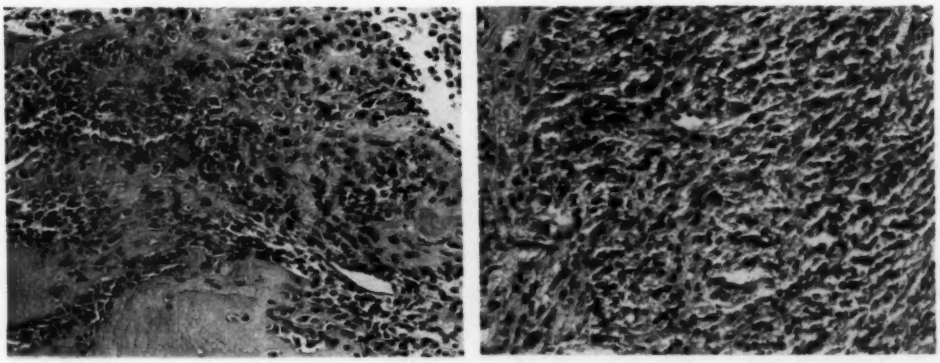


Fig. 4—Left: Irregular zones of osteoid tissue separated by zones of high cellularity; one portion of well formed bone. Right: Area in tissues formed by small spindle cells. Such areas were present marginally in region of invasion of soft tissue

mandible and the presence of a rounded, hard mass on the buccal aspect of the left side of the mandible in the molar region. Roentgenographic examination confirmed the diagnosis. A roentgenogram of the chest at this time showed the lung fields to be clear, but a nodular enlargement was present in the upper mediastinum. A needle biopsy of the mandible disclosed osteogenic sarcoma.

The patient was requested to enter the hospital for total resection of the mandible. This was carried out at another institution by Dr. Kiehn one month later. The operative result was reported as excellent three months postoperatively. Shortly after this, the patient had a sudden recurrence of the tumor on the left side of the jaw, and she subsequently died.[4] There was no autopsy.

CONCLUSIONS—At the initial operation the malignancy of the lesion was not suspected, and anterior resection was considered unjustifiably radical on the basis of the pathologist's report of osteoma. In the light of subsequent events, it is problematic whether even such a resection would have proved adequate to control the growth of the sarcoma. In the case reported by Dechaume and Baclesse[2] previously mentioned, roentgen therapy was instituted in three series of treatments rather than gross dissection. They state that such therapy served to reduce the attending discomfort for a period and to retard the progress of the tumor for a number of months, chiefly because it provided a zone of increased calcification. In view of the high malignancy of such tumors, they were skeptical of the value of deforming surgery. Their patient was reported to have lived approximately six years after the initial onset of the disease.

SUMMARY—A 48 year old woman came to the Cleveland Clinic because of an osteogenic sarcoma of the mandible which progressed unchecked after surgical treatment. An examination was made to determine the pathologic condition present, and the tumor was first believed to be an osteoma because of the abundant amount of well formed bone in the initial specimen. Despite anterior resection of the mandible at the second operation and subsequent total mandibulectomy, the patient died as the result of the neoplasm within a period of three years.

4. Kiehn, C. L. Personal communication.

■ MODERN EXPLORERS

Our scientists are our modern explorers, pushing back the frontiers of the "land of knowledge." This is a land not on this earth or in the heavens above, but composed of them and of the minds of men. It is a limitless land fraught with difficulties for the explorers. Towering mountains, rushing torrents, arid deserts, pestilent swamps, and tangled jungles must be penetrated and conquered. Unforseeable riches in well-being and material comfort are to be found. Perhaps even the "fountain of youth." *Ward Pigman, "Wanted: More Ivory Towers," The Scientific Monthly 80:255 April 1955.*

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Oral surgery and its relations with medicine

ORAL SURGERY has been officially defined by the American Dental Association as "that part of dental practice which deals with the diagnosis, the surgical and adjunctive treatment of diseases, injuries and defects of the human jaws and associated structures." Its scope has been further defined to include "the diagnosis, the surgical and adjunctive treatment of the diseases, injuries and defects of the human jaws and associated structures within the limits of the professional qualifications and training of the individual practitioner, and within the limits of agreement made at the local level by those concerned with the total health care of the patient."

These declarations were made after a careful analysis of the dental practice acts which are in force in the various states and consideration of the scope of oral surgery practice currently in vogue, and of the level of graduate training in oral surgery that is being provided at the present time. However, to make the definition sufficiently elastic and the scope sufficiently broad so that they apply in every locality, the final agreement regarding scope was referred to the local level. This decision, in each instance, is to be made by "those concerned with the total health care of the patient." This is, indeed, a broad concession and reflects great confidence in the graduate training and ability of oral surgeons to make themselves an integral part of each hospital organization. It also indicates a sincere trust in the honesty and ethics of our medical colleagues.

Unfortunately, a small minority group in medicine has instigated aggressive action in the House of Delegates of the American Medical Association designed to limit oral surgeons in their hospital work so that their efficiency, if not destroyed, would at least be greatly impaired. As a result, in 1953 the House of Delegates of the American Medical Association was influenced to adopt a resolution, including a unilaterally conceived definition of oral surgery, which was couched in narrow and confining language: "Dental-oral surgery is to be limited to the diseases of the teeth and jaws and lesions of the contiguous soft tissues related to the diseases of the teeth and jaws but excluding malignancies."

The Board of Trustees of the American Dental Association then informed the officials of the American Medical Association that their definition of oral surgery was wholly unacceptable, and that the dental profession would continue to practice in accord with the statutes of the various states. At a subsequent meeting between the Board of Trustees of the American Medical Association and representatives of the American Dental Association, however, the medical group readily agreed that, if the medical profession is to adopt a definition of oral surgery, the definition and scope as officially adopted by the American Dental Association was acceptable to them and should replace the definition made by their House of Delegates.

This report was presented in 1954 to the House of Delegates of the American Medical Association but, strangely, the House neither rescinded its previous definition nor adopted the one acceptable to and recommended by the Board of Trustees. Thus, a paradoxical situation was created in that the Board of Trustees of the American Medical Association has one definition of oral surgery and its House of Delegates has a conflicting one.

At the last meeting of the representatives of the two professions on February 5, 1955, the members of the medical group, with one lone exception, again indicated their acceptance of the definition and scope of oral surgery as adopted by the American Dental Association.

The dental profession has exhibited considerable patience with their medical confreres in this important matter, for negotiations have progressed at a painfully slow rate over a three year period. Much of the delay appears to be due to the influence of one small group of medical specialists, the members of which, until recently, have exhibited no interest in oral surgery nor had any training in that specialty.

The dental profession has developed oral surgery in the following step-by-step fashion over a period of many years.

1. It has historically pioneered in oral surgery.
2. It has developed the special field of oral surgery through formal undergraduate training, graduate study, contributions to the literature, and the institution of specialized practice in this field.
3. It has established the American Board of Oral Surgery which, through evaluation of candidates for certification for the past ten years, has elevated standards of graduate training.
4. It has the only scientific journal devoted solely to the field of oral surgery.
5. It has developed a steadily increasing number of graduate training services devoted entirely to oral surgery.

Medicine and dentistry have established such close cooperative working relations that it is inconceivable that either profession would allow a minority group within its ranks to disrupt that harmony and impair even slightly the further improvement of surgical care for the afflicted.

We are confident that medicine approves dentistry's educational efforts in oral surgery and dentistry's desire to elevate the standards of practice. The policy of making the scope of treatment in oral surgery dependent on the qualifications and training of the individual surgeon and within the agreements made at the local level by those concerned with the total health care of the patient is realistic and workable and should also receive approval of the medical profession.

Acceptance by the American Medical Association of dentistry's definition and declaration of the scope of oral surgery would immediately provide a background for improved standards for the specialty of oral surgery and greatly strengthen the working relations and professional bonds of the two professions—relations and bonds which must be of the highest order for the best interest of the patient.

■ Buccal eruption of a maxillary third molar may contribute to the development of an acutely painful temporomandibular joint. Since the buccally erupting tooth may impinge against the anterior surface of the ramus of the mandible, the patient soon develops an excursion of convenience in order to avoid contact between the ramus and third molar. Repeated excursions may result in an acutely painful joint. Simple extraction of the offending tooth usually will result in early relief of symptoms.

■ One of the complications which follow the use of palatal flaps for various oral surgical procedures is displacement of the flap by continued hemorrhage, edema or similar condition. Such a postsurgical complication leads to the formation under the flap of a hematoma which delays healing, causes increased postoperative pain and possibly contributes to postoperative infections. Various methods of holding the flap in place are currently in use, including sutures, wire frameworks and wire mesh-supported gauze. The use of an acrylic palatal splint, fabricated prior to surgery, has been found to be an excellent means of stabilizing these palatal flaps. This splint has greatly enhanced healing and has kept postoperative complications to a minimum. The splint is easily constructed from properly prepared maxillary models. When bony protuberances such as tori palatinus are to be removed, the area is trimmed from the cast prior to processing the splint. Extension of the splint into the interproximal embrasures usually affords sufficient retention, although in rare instances clasps may be utilized. The splint is inserted immediately after surgery and is worn until primary healing has occurred. It is removed daily for cleaning. The rapidity of healing and the increased comfort for the patient justify the additional time and effort needed for fabrication of the splint.

■ Errors in roentgenographic interpretation of the occlusal view of the maxilla often are made by taking the nasolacrimal canals for the posterior palatine foramens. These canals are situated in the side wall of the nose between the nasal cavity and the maxillary sinus. They are seen on the occlusal film as round, symmetrical, radiolucent areas medial to the molar teeth. The posterior palatine foramens usually are not seen in this occlusal view, as they are cast distally to the film by the angulation used. This observation can be substantiated by placing a wire in the nasolacrimal canals of a skull and exposing a routine occlusal view. The image of the wire on the film will be found just medial to the molars, and the posterior palatine foramens will not be seen.

■ One of the difficulties encountered in removal of upper third molars is lack of access. On occasion, this difficulty of accessibility is caused by the closeness of the coronoid process of the mandible to the maxillary tuberosity. Additional space often can be obtained by having the patient partially close the mouth and move the mandible toward the involved side. In this manner relaxation of the tissue is obtained, and the coronoid process is moved laterally, thus allowing more adequate access and visualization of the operative field.

■ A condition resembling geographic tongue is observed occasionally during pregnancy. Red macular areas, devoid of papillae, grow by peripheral extension. The lesions change from day to day. There is usually a slight burning sensation. The lesions require no treatment and will resolve spontaneously after parturition.

Readers are invited to send their clinical observations to the editor, Fred A. Henny, Henry Ford Hospital, Detroit.

■ Oral Manifestation of Leukemia

Q.—What treatment is recommended to provide comfort for patients suffering from oral manifestations of leukemia?

A.—There are various oral manifestations of the leukemias. Simple hyperplasias and edema of the gingiva usually are not accompanied by severe pain. The patients do not become uncomfortable until ulceration occurs, which leaves subcutaneous tissue exposed to the external environment of the mouth. In these instances, some means of covering the exposed connective tissue or anesthetizing the nerve endings is indicated.

Thorough drying of the mucosa and application of tincture of benzoin is highly efficacious in relieving pain. The drug should be allowed to dry on the mucosal surface before saliva is allowed to come in contact with it. This procedure provides a covering for the exposed connective tissue and seals off the nerve endings. A 0.25 per cent spray of tetracaine hydrochloride (Pontocaine), used in an atomizer, will anesthetize the nerve endings and relieve pain, but it also eliminates the taste sensation. The new local anesthetic agent lidocaine hydrochloride, 2 per cent in solution of carboxymethylcellulose 2.5 per cent (Xylocaine Viscous), should be highly effective.

■ Sequence for Extractions

Q.—When upper and lower teeth are to be extracted at the same time, is there a preferred sequence for the extractions?

A.—The sequence is a matter of personal preference. Some surgeons feel that if the upper teeth are extracted first, blood from this operative field will obscure the lower arch. Hence they prefer to extract the lower teeth first. Others prefer to extract the upper teeth first. There is less chance of particles of tooth, broken fillings, bone and debris falling into the lower sockets if extraction of the lower teeth is left to the end of the procedure.

■ Surgical Exposure of Imbedded Teeth

Q.—Are there any specific precautions to be followed in surgical exposure designed to encourage the eruption of an imbedded tooth?

A.—Many orthodontists now believe it is unwise to expose impacted teeth unless the opening can be maintained. They feel the scar tissue that forms after removal of bone over the crown of the tooth offers greater resistance to eruption than the original bone. Hence, if the crown is to be exposed, the opening should be maintained by surgical packs or dressings until the orthodontist can attach his appliance or until the tooth erupts into the mouth of its own accord.

■ Submaxillary Sialolith

Q.—What are the possible complications from the intraoral removal of a submaxillary sialolith?

A.—Varying amounts of pain usually accompany the procedure, and any operative wound

This section devoted to queries and comments from readers on topics of current interest to oral surgeons and general dental practitioners, is edited by James R. Hayward, University Hospital, Ann Arbor, to whom readers are invited to send their communications. The answers, prepared by competent consultants, do not necessarily represent the opinions of any official scientific organization. Your participation in this section is invited.

The Editor

in the floor of the mouth carries the constant threat of infection. With present-day therapy, these complications are minimal. More serious complications are hemorrhage, injury to the lingual nerve, diffusion of saliva into the surrounding soft tissue and stenosis of the duct. In removing deeply seated sialoliths, there is a possibility of injury to the external maxillary artery, which may be accompanied by profuse hemorrhage. This hemorrhage usually can be controlled by pressure. The lingual nerve passes close to the mandible in the region where the incision must be made to remove some of these sialoliths, and care must be exerted to avoid this structure. After removal of the sialolith, deeply placed sutures might close off the duct and the normal pathway of evacuation of the gland. This closure may result in the diffusion of saliva into the surrounding soft tissue, occasionally into the lateral pharyngeal spaces and into the soft palate. Diffusion can be relieved by removing the suture. In extremely rare instances complete stenosis of the duct may be an aftermath of the surgery. When this occurs, it is generally necessary to remove the gland.

■ Diagnosis of Hemangioma

Q.—When clinical symptoms suggest the presence of a hemangioma in the soft tissues of the face and oral cavity, what aids may be used to verify the diagnosis?

A.—Hemangiomas of the soft tissue usually are evident from clinical examination. If, when the patient's head is placed in a dependent position and he "strains" for a short period of time, the lesion becomes engorged and enlarged, it is probably a hemangioma. Aspiration of blood from a compressible lesion also points to a vascular lesion. In determining the extent of a hemangioma, it is advantageous to evacuate the mass by aspiration with a large needle and syringe and then to fill the lesion with iodopyracet (Diodrast). Roentgenograms taken immediately after this procedure will indicate the extent of the lesion.

■ Penicillin Allergy

Q.—Approximately two weeks after the treatment of a severe oral infection with penicillin, a patient suddenly developed multiple blood-filled vesicles on his arms and hands. Can you tell me what they represent and how they should be treated?

A.—The condition described is known as a hemorrhagic bullous eruption and is one of the rare and bizarre manifestations of a penicillin allergy. It is an alarming manifestation but not particularly dangerous. The drug should be withdrawn and an antihistamine administered. If the symptoms are severe, cortisone therapy may be necessary. The lesions usually resolve in ten days to two weeks.

■ Removal of Four Impacted Teeth

Q.—Is it permissible to remove four impacted teeth at one time?

A.—Many factors must be taken into consideration; the age and attitude of the patient, ability of the operator and the time available for convalescence. If the patient is cooperative and if the operator has sufficient experience to insure that the surgical procedure will be as atraumatic as possible, it is best to remove all impactions at the same time. The patient seems to have little more reaction from removal of four impactions than from the removal of two, and the postoperative pain is no more severe. Patients usually are grateful that they do not have to return for further surgery.

■ Oral and Dental Diseases. By Hubert H. Stones, M.D. Third edition. 1,019 pages with 965 illustrations. Index. Price $18. Baltimore, The Williams & Wilkins Co., 1954.

The major revision of the third edition of Dr. Stones' book is in the section on the nervous system and muscles. The book is still an excellent text for use by dental students, both on the undergraduate and graduate level. It is encyclopedic in scope in that it contains some material on almost all diseases and malformations of the oral cavity. The book is well thought out, and its divisions for study are logically presented.

The chapter on congenital malformations of the jaws and associated parts is particularly well done, and it contains some excellent photographs and illustrations which are not seen in other texts devoted to this subject.

A fine chapter, and up to date, is the one on the effects of endocrine disorders on the development of the jaws and oral cavity. Also deserving of mention are the chapters devoted to malocclusion, maldevelopment and abnormalities of the oral structures, treatment of infections of the face and neck and that on stomatitis and allied diseases, which contains excellent photographs and illustrations.

The chapter on maxillofacial injuries possibly could have been extended to indicate treatment by the open method as well as by the closed methods illustrated in the text. The bibliography will supplement the material.

Dr. Stones classifies tumors of the jaws in two large categories—odontogenic and nonodontogenic. Under these two large classifications, he discusses the benign and malignant tumors of the jaw bones. A chapter is devoted to the tumors of soft tissues of the oral cavity. The histopathologic slides, some of which are in color, are representative of the lesions. The chapter on the diseases of the salivary glands includes tumors of the salivary glands and is acceptable in every respect.

This excellent reference will not answer all the questions which might arise, but it will, at least, give a preliminary statement and will, by means of its excellent bibliography, lead the student to proper sources for his answers.—*Marvin Revzin.*

■ Social Science in Medicine. By Leo W. Simmons, Ph.D., and Harold G. Wolff, M.D. 254 pages. Index. Price $3.50. New York, Russell Sage Foundation, 1954.

In this book an appeal is made to the medical profession to aid in the integration of biological and sociological knowledge. The physician who relies on the biophysical sciences also deals daily with an abundance of psychosocial data.

The editors call attention to the serious liabilities of the present-day use of hospitals, the loss of the leisurely personal contact between staff and patient and the housing of large numbers of gravely ill persons, a condition which has produced special risks both physical and psychosocial. Assembly line methods increase the likelihood of oversights and make difficult the orientation of patient care around individual needs.

Although it has long been apparent that medicine and social science are equally concerned in their special way with human behavior, medicine has devoted itself mainly to those aspects of behavior which involve pain, physiological and organic responses—those phenomena, in short, that threaten the survival or comfort of the individual.

Social science, on the other hand, has been preoccupied with the study of man in his social environment—the way in which social

relationships are organized and carried on, the interaction of persons with different status and roles and the relationship of all these to individual or social survival. To produce the most desirable cooperation between medicine and the social sciences, certain prerequisites must be met, one of which is the alerting of personnel of both disciplines to the areas of common concern.

The Russell Sage Foundation has as its current program the improvement of utilization of social science research in professional practice. This book ably demonstrates how these disciplines have advanced to a point where fruitful collaboration between medical scientists and social scientists is feasible and is in process of development. The book should be read by public-spirited citizens who share responsibility for health and welfare programs. —*R. M. Walls.*

■ PSYCHOLOGY OF PHYSICAL ILLNESS. Edited by Leopold Bellak, M. D. 231 pages. Index. Price $5.50. New York, Grune & Stratton, 1952.

This small volume attempts to integrate psychiatric knowledge into other fields of medical practice. Twelve medical specialties and dentistry are covered by men with dual experience in psychiatry and their specialties. The essays are essentially clinical, with the subject range necessitating a condensed, rather superficial approach.

Readers of the JOURNAL OF ORAL SURGERY will be most interested in the last two chapters, "Psychological Aspects of Dentistry" and "Personality of the Physician."

In the former, Sol. J. Ewen has crammed a tremendous range of information into 21 pages. He covers both the emotional and intellectual aspects of the mouth. His case histories are well chosen.

It seems to this reviewer that he tends, however, to stress the "state of dependency" which occurs in the dental chair, and, corollary to that, minimizes the technics which assist the patient to acquire an active mastery over his anxiety.

Leon Altman concludes the book with suggestions for soul searching relative to the physician's personality. He stresses that one must be aware of feelings toward patients "before one can work with them accurately or with ease and composure."—*Elizabeth Levitin.*

■ PLASTIC SURGERY AT THE NEW YORK HOSPITAL 100 YEARS AGO. By Herbert Conway, M.D., and Richard B. Stark, M.D. 110 pages with illustrations and bibliography. Price $5. New York, Paul B. Hoeber, Inc., 1953.

This is the story of the development of plastic surgery in the middle of the nineteenth century with a brief biographical sketch of Gurdon Buck, a surgeon of that period. Dr. Buck is best known for "Buck's extension," a procedure which used traction in the treatment of fractures of the femur. His book *Contributions to Reparative Surgery* published in 1876 established him as a pioneer in reconstructive surgery.

The treatise contains several detailed descriptions by Dr. Buck of various operative technics for plastic reconstruction of the face. One case report deals with the repair of maxillofacial tissue extensively destroyed by gangrene. Dr. Buck generously acknowledges his reliance on "Mr. Thomas B. Gunning, a skillful dentist" for the construction of an ingenious appliance for the patient. This preoperative prosthesis was indispensable to the treatment plan, and Dr. Buck describes its design and function in highly complimentary terms.

Dr. Buck outlined principles for the use of relaxation incisions, pedicle flaps and the rotation and advancement of soft tissue flaps. He advocated the use of multiple, fine sutures and practiced their early removal. His approach to the problems of plastic repair may be considered fundamental to modern concepts of treatment.

This book will make enjoyable reading for those interested in the historical background of surgery in the Civil War era. Despite the limitations of knowledge and experience of those days, the results achieved deserve our admiration and respect.—*James Springer.*

■ X-Ray Examination of the Mandibular Condyle. G. Beal, Commissionat and Yardin. Rev. de Stomatol. 55:821 Oct. 1954.

A transorbital method may be used for roentgenographic examination of the mandibular condyle. The film is exposed with the patient's mouth open so as to avoid superimposition on the condyle image of other bony structures. The condyle and articular interspace appear with a definite outline in a frontal plane. In some instances, this method may be used to advantage with an arthrogram as described by Norgaard.

The method has proved to be of special value for examination of fractures of the condyle, in temporomandibular arthrosis, in temporomandibular joint ankylosis and for the study of other pathologic conditions and abnormalities of the condyle.—*Jacques Levignac.*

■ Correct Time and Sequence for Closure of Cleft Lip and Palate. Louis W. Schultz. Am. J. Surg. 87:651 May 1954.

Controversy on the proper time for closure of a cleft lip and palate is due, in part, to the influx of new men in the various branches of medicine, dentistry and speech therapy. The majority of plastic surgeons operate on cleft lips when the patient is two or three weeks old. The closure of the palate is accomplished at approximately two years of age. As a rule, the lip should be closed at about two weeks of age and a closure of the palate should be performed at three to six months. If surgery has not been performed on a child six months to two years old, the palate should be closed first so the patient may have the optimum advantage of an early closure of the palate and resultant perfect speech.

Bilateral cleft lips and palates, as a rule, must be handled a little differently. In these cases the intermaxillary segment of bone and lip tissue usually project from the tip of the nose. The best results are obtained by closing the bilaterally cleft lip on both sides at once. This method produces pressure on the intermaxillary segment of bone, causing it to move slowly between the two maxillary segments. The closure of the lip should be followed in three to six months by a closure of the palate. The main reason for early closure of palates is the good healing obtained at this age, with subsequent normal health and speech.

An acute or chronic otitis media in a child born with a cleft palate is a definite indication for closure of the palate as early as possible, the acuteness, chronicity or temperature of the patient notwithstanding. The otitis media clears immediately postoperatively, and the baby becomes afebrile. Surgery at two to six months is definitely indicated in the child that is born with a cleft palate associated with a micrognathia. Surgery produces a normal vault which allows the tongue to rest against the soft palate, thus leaving the normal nasopharyngeal opening for breathing through the nose. Suggestions for facilitating the technic of early closure are listed.—*Myron Kaufman.*

■ Restoration of Lip Contour Using Fascia, Tendon, and Dermal Grafts. Kenneth Pickrell, M.D.; Frank Masters, M.D.; Nicholas Georgiade, D.D.S., M.D., and Charles Horton, M.D. Plast. & Reconstruct. Surg. 14:126 Aug. 1954.

A fascia graft in the form of a long strip from the tensor fascia lata is possibly the graft of choice because of its ready accessibility, ease of removal, unlimited supply and ability to glide when implanted. A tendon graft, either the palmaris longus or the flexor digitorum sublimis from the fourth finger and forearm may be removed without causing any dysfunction or

disability. The peroneus brevis may be used also, but the peroneus longus should not be removed because it stabilizes the foot. With the exception of the dorsi-flexor of the great toe, which should not be removed, the remaining tendons of the lesser toes may not be of sufficient size and bulk unless several are used. Dermal grafts are not as satisfactory as either fasciae or tendons because of their inability to glide and function as a mobile structure.

A small incision is made in the skin just superior and lateral to each oral commissure. Each incision is deepened to expose the orbicularis oris muscle. Using a blunt pointed iris scissors, a tunnel is dissected across the entire lip, connecting the two incisions. This tunnel should be located just above the vermilion border and should be of sufficient size to admit a Kelly clamp freely from either side and without any points or area of "hand."

If a fascial graft is to be inserted, the strip is folded on itself to obtain a triple thickness. If a tendon graft is to be used, it is folded only once to obtain a double thickness since it is considerably thicker and heavier than fascia. A suture of no. 0000 white silk is then inserted into each end of the folded fascia or tendon, and the ends are left long. A mosquito clamp is inserted through the lip tunnel, and the tip of the clamp is made to appear through the opposite side. The graft is drawn through the tunnel. It is important to make certain that the graft will slide with ease.

The most important maneuver in the operation is as follows. A temporary suture is placed in the mucous membrane of the buccal surface of the lip just above the frenulum. The lip is retracted superiorly under tension so that the center of the lip is drawn up almost to the tip of the nose, and the philtrum is brought against the columella. In so doing, a triangle is formed whose apex is in the center of the lip, the lateral limbs are formed by the right and left sides of the lip, while the base is located in the buccoalveolar sulcus or on a line from one oral commissure to the other.

Elevation and extension of the lip in this manner will convert a flat lip into one with an exaggerated arc. By this maneuver, the protruding ends of the graft will be drawn into the original incisions on each side of the lip. The tension of the traction suture is not released, the original suture of white silk which was placed in the ends of the graft is now used to anchor the fascia or tendon to the orbicularis oris and buccinator muscles on each side. The incisions in the lip are closed in two layers.—*Irwin A. Small.*

■ FRACTURES OF THE CONDYLE. M. DeChaume and C. Crepy. Rev. de Stomatol. 55:861 Oct. 1954.

A follow-up study has been made of 50 fractures of the condyle. The fractures are classified according to type as follows: intraarticular fractures; extraarticular fractures, including fractures with light displacement and those with considerable overriding or dislocation; bilateral fractures of the head and of the neck of the condyloid process; fractures of the condyle associated with other fractures of the mandible.

The study shows that treatment of these fractures should be an orthopedic one. Surgery is almost never required and should be postponed until failure of the recommended orthopedic method.

Even the poor anatomic result observed fairly often in instances of fracture dislocations of the condyle causes only a slight disturbance in function. This study corroborates the observation of Sebileau that the temporomandibular joint recovers and adjusts to new conditions with only a minimal disturbance in the jaw's mechanism.

The results acquired were satisfactory in most instances when the jaws were wired together for three weeks, provided there was good occlusion. Less satisfactory results were observed when poor occlusion existed. The most unsatisfactory results were observed in instances of bilateral fractures of the condyle. A long follow-up study of each patient is necessary.—*Jacques Levignac.*

Announcements

■ American Society of Oral Surgeons to Meet In October

The American Society of Oral Surgeons will meet October 11-14 in Los Angeles. Harry M. Seldin is president of the group.

■ Association to Ask A.M.A. to Rescind Oral Surgery Definition

Among the actions of the Association trustees at their March 31 to April 1 meeting in Chicago was a decision to make a formal request to the A.M.A. Board of Trustees that the House of Delegates of the A.M.A. rescind its definition of oral surgery. The Trustees decided also to publish an information bulletin on the oral surgery problem to be sent all members of the American Dental Association. These actions followed a report of the Special Committee on Problems in the Field of Oral Surgery.

■ First Subscription In For New Abstract Journal

On May 4 the first subscription to DENTAL ABSTRACTS, the new journal of abstracts from the world dental literature, was received in the Association's Central Office. It came from Maurice N. Stern, editor of the Tenth District Dental Society Bulletin, Forest Hills, N. Y.

The first issue of the new publication, the only one of its kind in the dental field, is scheduled for January 1956. The subscription rate is six dollars for domestic readers; seven dollars for subscribers from abroad.

DENTAL ABSTRACTS will contain summaries from English language journals and will abstract also from articles printed originally in German, French, Swedish, Italian and Spanish. In commenting on the launching of the publication, Lon W. Morrey, Association editor, said, "This is an unequaled opportunity for the practicing dentist to have at his fingertips the latest developments in dental science and dental practice from all over the world." The editor pointed out that nearly 2,000 dental articles are published throughout the world each month.

"It is impossible for anyone to keep abreast of all the important contributions to the literature," Dr. Morrey said. "Thus, by providing in a short reading period each month a survey of dental progress throughout the world, DENTAL ABSTRACTS will provide the answer to a long-standing need."

■ Program Planning Begun For Annual Meeting

An appeal has been made to secretaries of the dental societies, deans of the dental schools, heads of the federal dental services and other organizations in the dental field requesting material for possible presentation on the scientific program of the Association's 96th annual session in San Francisco October 17-20. In the appeal Charles S. Kurz, chairman of the Council on Scientific Session, called attention to the popularity of the projected clinics at the Miami meeting. He pointed out also that the Council is scheduling an extensive program of table clinics and "is particularly interested in study groups which might present a group clinic."

At the same time, Donald Washburn, director of the scientific exhibit, announced that letters have gone out inviting applications for exhibit space. Requests should be made early, Dr. Washburn stated.

All scientific sessions will be held in the Civic Auditorium, it has been announced. The Board of Trustees and the House of Delegates will meet in the Fairmont Hotel. Also at the Fairmont will be the luncheon for international guests. The state officers' conference is scheduled for the Mark Hopkins, the ladies' luncheon and fashion show at the Sheraton Palace. The banquet honoring President Daniel F. Lynch will be held at the Sheraton Palace also.

All housing for the annual session is handled through the Association Housing Bureau, which opens April 1 at 61 Grove St., San Francisco 2.

■ Need Seen for Integration In Teaching of Anesthesia

A greater degree of integration is needed in the teaching of local anesthesia by the dental schools, according to participants in a conference on local anesthesia in dentistry held March 20 in the Central Office. The conference, sponsored by the Council on Dental Therapeutics and the Council on Dental Education, was attended by members of the two councils and representatives of nearly all the dental schools.

At a date to be announced later, a conference on general anesthesia will be held. To be discussed are the content of undergraduate and graduate courses in general anesthesia, the time that should be spent on them and the best methods of teaching. Attention will be given also to the amount of teaching in general anesthesia that should be included at the undergraduate level.

■ List Problems of Dentistry to Be Discussed By F.D.I.

Hospital dental services, dental education and the dental services of the Armed Forces of various countries will be on the agenda of the August 14-20 annual meeting of the Fédération Dentaire Internationale. The meeting is scheduled for Copenhagen, Denmark. In addition to the general assemblies of delegates from the national member associations, the F.D.I. councils and commissions will meet. An extensive scientific program of films, lectures and panel discussions is planned as well as a special workshop of experts in periodontology.

Further information on the meeting and on hotel reservations can be obtained from Dr. Klausen, 1, Alhambravej, Copenhagen 5, Denmark.

■ American Institute of Dental Medicine Meets in October

October 23-27 are the dates of the next annual meeting of The American Institute of Dental Medicine. The meeting will be held at the Desert Inn, Palm Springs, Calif. On the faculty will be Maury Massler, University of Illinois; Valy Menkin, M.D., Temple University Medical School; Hans Selye, M.D., University of Montreal; Reidar F. Sognnaes, D.M.D., Harvard School of Dental Medicine, and Wendell L. Wylie, University of California.

Applications and full information on the meeting may be obtained from Miss Marion G. Lewis, 2240 Channing Way, Berkeley 4, Calif.

■ Schools Announce Oral Surgery Programs

A rotating internship in dentistry is offered by the College of Physicians and Surgeons in San Francisco. The course provides work in the hospital in conjunction with the graduate oral surgery program and courses in precision casting, complete denture prosthetics, gold foil, endodontics, dentistry for children, tooth guidance, oral roentgenology and local anesthesia.

"The Use of Oral Surgical Instruments" is the title of a home study dental seminar kit designed by the University of Minnesota dental school in Minneapolis. The kit, which may be rented for five dollars plus mailing costs, contains a file of photographic slides, a slide viewer, a record and text of the lecture.

■ Form Northwest Society of Oral Surgeons

The Northwest Society of Oral Surgeons has established its headquarters in Seattle, announces Thomas J. McIntyre, society secretary-treasurer. The group is engaged in expanding its membership to all oral surgeons in Washington. Persons interested are asked to write to Dr. McIntyre, 744 Stimson Bldg., Seattle 1.

Frederick H. Francis is president of the society, Jack C. Garretson, vice-president.

■ German Association Schedules July Meeting

The German Association for Maxillo-Facial Surgery will hold its scientific session in Hamburg July 26-29. International visitors are welcome. Information on the meeting may be obtained from the secretary, Fritz Schön, Ludwigstrasse 30, (13b) Bad Reichenhall, Bayern, Germany.

Editorial communications

■ ORIGINAL COMMUNICATIONS—This journal invites concise original contributions in the broad field of clinical and experimental surgery of the mouth and associated structures, including roentgenology, diagnosis, anesthesia and oral surgical pathology. Articles are accepted for publication with the understanding that they are contributed solely to the JOURNAL OF ORAL SURGERY. All manuscripts are subject to editorial modification. Neither the editors nor the publishers accept responsibility for the views and statements of authors expressed in their communications.

■ MANUSCRIPTS—Manuscripts submitted for publication should be sent to Fred A. Henny, Editor, Henry Ford Hospital, Detroit, Michigan.

Manuscripts should be typewritten on one side of the paper only with double spacing and liberal margins. The author's name and the abbreviated title of the article should appear at the top of each manuscript page. The original should be sent to the editor and a carbon copy retained by the author. Manuscripts will not be returned if accepted for publication.

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